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ОПЫТ ЛЕЧЕНИЯ БОЕВЫХ РАНЕНИЙ МАГИСТРАЛЬНЫХ АРТЕРИЙ КОНЕЧНОСТЕЙ В УСЛОВИЯХ ГРАЖДАНСКОГО МНОГОПРОФИЛЬНОГО СТАЦИОНАРА
EXPERIENCE IN TREATING COMBAT WOUNDS OF THE MAIN ARTERIES OF THE EXTREMITIES IN A CIVILIAN MULTIDISCIPLINARY HOSPITAL

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ANESTHESIA MANAGEMENT FOR NEPHRECTOMY WITH INFERIOR VENA CAVA THROMBECTOMY. PERIOPERATIVE CONSIDERATIONS

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КЛИНИЧЕСКИЕ СЛУЧАИ

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The Experience of Treating Battle Injuries of the Magistral Arteries in the Limbs in the Settings of the Civilian Multi-profile In-patient Hospital

S.V. Deryabin[1], A.V. Smirnov[1], R.I. Khabazov[1], P.Yu. Orekhov[1], P.Yu. Parshin[1], A.R. Abasov[1], M.V. Khruslov[2], A.V. Troitskiy[1]

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ABSTRACT

BACKGROUND: *The modern military conflict is characterized by a significant number of wounded with the damage of the magistral arteries in the limbs. Such an injury is accompanied by the possibility of lethal outcome and by the high risk of limb amputation. The treatment of the injuries in the major arteries requires high qualification of the medical staff and sufficient equipment basis. The optimal tactics for this still remains the matter of discussion.* ***AIM:*** *to define the specific features of the surgical tactics in cases of injured magistral arteries in the settings of the civilian specialized in-patient hospital in the regions adjacent to the scene of military operations.* ***METHODS:*** *The analyzed data included the treatment results in 57 patients with battle injuries of the magistral arteries in the limbs, in which we have managed to track the direct result of restoring the arteries within not less than two days. The variety of manifestations observed in cases of injuries was demonstrated using 8 clinical cases. The surgical tactics was defined by the degree of ischemia in the muscles and the extent of damaging the tissues in the limb. Amputations were conducted in cases of developing the ischemic contracture or in cases of significantly damaged limb tissues.* ***RESULTS:*** *The resection of the artery with autovenous prosthetic replacement was done in 49 cases, while the circular resection of the artery with the direct anastomosis — in 8 cases. Within the earliest post-surgery period (first two days) due to the post-ischemic syndrome, the usage of the extracorporeal detoxication methods was required in 5 (9%) wounded. The restoration of the peripheral circulation was observed in 56 (98.2%) cases, the secondary amputation of the lower limb was done only in 1 (1.8%) operated patient. No fatal outcomes were reported (0%).* ***CONCLUSION:*** *In the modern military conflict, the battle contact line can be located in the direct proximity from the well-equipped civilian healthcare institutions, at the premises of which the high-tech medical aid is accessible. Our experience shows that, in case of performing the complex surgeries, the follow-up within the early period is practicable to be organized at the site with avoiding the immediate evacuation. In cases of damaging the magistral artery in the limb, the main parameter affecting the possibility of saving the limb itself, is the degree of ischemia in the muscles. The irreversible ischemia is often hard to define and the development of the ischemic contracture should be taken as the guidance. The time of injury, the absence of pulse, of the active movements or sensitivity cannot serve as an indication for amputation. The algorithm developed by us has shown its high efficiency.*

Keywords: *acute ischemia of the limb; injuries of magistral arteries; battle injury; limb amputation; prosthetic replacement of the vessel.*

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BACKGROUND

The modern armed conflict has a number of specific features, which significantly affect the type of limb injuries and the medical aid needed by the wounded and the injured. New types of armament with special characteristics of the damaging elements specify the unique types of wounds differing from all the ones described during the previous armed conflicts, with this, the battle contact line can be located at the direct proximity from the well-equipped large-scale civilian healthcare institutions, in which it is possible to provide the specialized and the high-tech medical aid. The

Опыт лечения боевых ранений магистральных артерий конечностей в условиях гражданского многопрофильного стационара

С.В. Дерябин[1], А.В. Смирнов[1], Р.И. Хабазов[1], П.Ю. Орехов[1], П.Ю. Паршин[1], А.Р. Абасов[1], М.В. Хруслов[2], А.В. Троицкий[1]

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АННОТАЦИЯ

Обоснование. *Современный военный конфликт характеризуется значительным числом раненых с повреждениями магистральных артерий конечности. Такая травма сопровождается возможностью летального исхода и высоким риском ампутации конечности. Лечение ранений крупных артерий требует высокой квалификации медицинского персонала и достаточной оснащённости. Оптимальная тактика при этом до сих пор остаётся предметом дискуссий.* ***Цель*** *— определить особенности хирургической тактики при повреждениях магистральных артерий в условиях гражданского специализированного стационара в районе вблизи проведения боевых действий.* ***Методы.*** *Проанализированы результаты лечения 57 пациентов с боевыми ранениями магистральных артерий конечностей, у которых удалось отследить непосредственный результат восстановления артерий в течение не менее двух суток. Многообразие проявлений ранений продемонстрировано на 8 клинических примерах. Хирургическую тактику определяли степень ишемии мышц и массивность поражения тканей конечности. Ампутации выполняли при формировании ишемической контрактуры либо при значительных поражениях ткани конечности.* ***Результаты.*** *Резекция артерии с аутовенозным протезированием выполнена в 49 случаях, циркулярная резекция артерии с прямым анастомозом — в 8. В ближайшем послеоперационном периоде (первые двое суток) в связи с постишемическим синдромом применение методов экстракорпоральной детоксикации потребовалось 5 (9%) раненым. Восстановление периферического кровотока отмечено в 56 (98,2%) случаях, вторичная ампутация нижней конечности выполнена только 1 (1,8%) прооперированному пациенту. Летальности не было (0%).* ***Заключение.*** *В современном военном конфликте линия боевого соприкосновения может находиться в непосредственной близости от хорошо укомплектованных гражданских учреждений здравоохранения, на базе которых возможна высокотехнологичная медицинская помощь. Наш опыт показывает, что в случае выполнения сложных хирургических операций наблюдение за пациентом в ближайшем периоде целесообразно организовать на месте и воздержаться от немедленной эвакуации. При травме магистральной артерии конечности основным параметром, влияющим на возможность сохранения самой конечности, является степень ишемии мышц. Необратимую ишемию зачастую определить затруднительно и ориентироваться следует на формирование ишемической контрактуры. Время получения ранения, отсутствие пульса, активных движений и чувствительности не могут служить показанием к ампутации. Разработанный нами алгоритм показал высокую эффективность.*

Ключевые слова: *острая ишемия конечности; ранение магистральных артерий; боевая травма; ампутация конечности; протезирование сосуда.*

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majority of available publications on the battle-field surgery is devoted to the operations of the military hospitals of various levels, while the experience of the civilian institutions re-profiled for providing the medical aid to the servicemen, is practically not disclosed, while the developed Methodical Guidelines on the battle-field surgery do not take into account the specific features of the civilian multi-profile in-patient hospital [1, 2].

The institutions within the system of the Federal Medical-Biological Agency of the Russian Federation (FMBA of Russia), located near the areas of military operations, provide the aid to the wounded and injured from the first day of the conflict. The reinforcement of the local medical teams has resulted in the formation of the joint team of the FMBA of Russia, consisting of the highly qualified vascular surgery specialists of the Federal State Budgetary Institution "Federal Scientific and Clinical Center for Specialized Types of Medical Care and Medical Technologies under the Federal Medical-Biological Agency" (FSBI FSCC FMBA of Russia).

The trauma of the major vessels in the limbs is oftentimes the most critical injury and it is accompanied by not only the risk of amputation, but also by the possibility of lethal outcome [3, 4], due to which, the main tasks of the vascular surgeons are saving the life and salvaging the limb. Conducting the vascular reconstruction in cases of irreversible limb ischemia can further lead to the rhabdomyolysis and to the acute renal failure. The key prognostic parameter which should be used as the guidance when selecting the surgical tactics is the degree of muscle ischemia on admission and the predicted worsening of the ischemic burden, however, the objective evaluation of this parameter often presents serious difficulties.

Research aim — to define the specific features of the surgical tactics in cases of damaged magistral arteries of the limbs in the settings of the civilian specialized in-patient hospital operating in the area located near the field of military operations.

METHODS

Research design

This was a retrospective observational research of the hospital cases of treating the battle injuries of the magistral arteries in the limbs at the premises of the civilian re-profiled in-patient hospital.

Conformity criteria

Inclusion criteria: patients with battle trauma, admitted to the in-patient unit, which were diagnosed and operated due to the damage of the magistral arteries of the limbs along with tracking the direct result within not less than two days from the moment of the surgical intervention.

Non-inclusion criteria: the presence of the leading (dominating) combined trauma in other areas.

Medical procedure description

The patients were admitted both as the result of arranged evacuation after having received the medical aid provided by the front-line medical groups and directly after being injured and after being evacuated with the aid of the volunteers. On admission to the in-patient hospital, at the level of the admission department each patient was quickly examined by the multidisciplinary team of specialists consisting of the vascular surgeon, the trauma specialist, the neurosurgery specialist and other specialists depending on the type of wounds. In cases of detecting the signs of on-going hemorrhages and impaired vital functions (consciousness, hemodynamics, respiration) or in case of detecting the triad of death (hypothermia, acidosis and coagulopathy), the intensive therapy headed by the anesthesiologist-intensivist was initiated at once at the admission ward and the patient was immediately transported to the operation room.

Methods for registration of outcomes

If the status of the patient was applicable, at the level of the admission department, diagnostic procedures were arranged, combined with the basic laboratory and instrumental examinations. If necessary, the duplex ultrasound scanning (DUS) of the vessels was done along with the computed tomography (including the contrasting). The DUS was also performed intra-operatively.

In cases of damaged major vessels of the limbs, the clinical examination included the determination of the degree of limb ischemia based on the modified classification by V.A. Kornilov (table 1) and on the classification by I.I. Zatevakhin [2]. The following parameters were evaluated: sensitivity, active and passive motions, presence of pulse in the peripheral arteries and the data from the instrumental methods of examination. The surgical tactics was determined on an individual basis and based on the Methodical Guidelines on the battle-field surgery from the Main Military Medical Directorate under the Ministry of Defense of Russia (see table 1).

Table 1

The classification of acute limb ischemia in cases of wounds*

Degree of ischemia		Main clinical signs			Doppler signal		Prognosis	Surgery tactics
		Sensitivity	Active motions	Passive motions	Arterial	Venous		
Compensated (due to the presence of collateral vessels)		+	+	+	+	+	No risk of gangrene	No indications for emergency restoration of the artery; the ligation of the vessel is safe
Non-compensated	Early	+/-	+/-	+	+/-	+	The limb necrotizes within the nearest 6–8 hours	Emergency prosthetic replacement or restoration of the artery is indicated, along with the preventive fasciotomy
Non-compensated	Critical (with the duration of more than 6 hours)	-	-	+/-	-	+	Direct threat to the viability of the limb	Emergency temporary prosthetic replacement of the artery is indicated, along with the therapeutic fasciotomy, if possible — plasmapheresis
Irreversible (ischemic contracture)		-	-	-	-	-	Salvaging the limb is impossible	Indications for arranging the amputation, for the attempts to restore the artery can result in the death of the wounded due to the endotoxicosis

Note. * — cited as per [2].

In case of irreversible ischemia or significant destruction of the limb tissues, the primary amputation was done. In cases of the compensated and the uncompensated ischemia, vascular reconstructive interventions were arranged. The damaged area of the arterial vessel was resected, depending on its length with forming the direct anastomosis or with conducting the autovenous prosthetic replacement with the reversed segment of the great saphenous vein (*vena saphena magna*) or using the basilic vein (*vena basilica*). In case of detecting the damage of the major veins, if possible, they were sutured, if not — ligated. If necessary, the simultaneous fasciotomy was arranged in the lower limb. The surgical technique used for the fasciotomy was the classic semi-occlusive variant: from 1–3 single incisions with length of 2–3 cm at the border between the upper and the middle third of the shin, the fascial sleeve was opened and the Metzenbaum scissors were used to dissect the fascia in the projection area of fascial sleeves at the distal and the proximal directions.

Anticoagulant therapy in the standard variant included the subcutaneous administration of enoxaparin sodium 4000 anti-Xa IU twice daily.

Upon the progression of the post-ischemic syndrome, the methods of extracorporeal detoxication were used along with the secondary amputation of the limb.

RESULTS

Research sample (participants)

The direct treatment result was accessible for tracking in 57 wounded.

We have followed-up the damage of the major vessels in the limbs in 18% of the admitted wounded, however, due to various reasons (agonal state; significant destruction of the limb tissues; the dominant contribution of the trauma in another area; the formation of the ischemic contracture in the major joints etc.), the vascular reconstruction procedures were carried out in less than 1 out 5 of such patients. In many cases, there was no full trackability of even the direct result due to the evacuation to the next stage of providing the medical aid resulting from the need to clear the bed capacity in the settings of the continuous flow of wounded.

The type of vessel wounds directly depended on the type of the damaging element. Only in 2% of observations, the reconstructive vascular surgery was

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done due to the bullet wounds. In the absolute majority of cases, the cause was the mine-blast trauma, with only 33% operated patients having the damage caused by the primary damaging factors of the explosion (the detonation products and the blast wave), while the other observations were only the wounds caused by the secondary damaging elements (shell fragments).

Primary findings

Small fragments sized up to 1 cm (in 49% of the operated individuals), generally, were causing the perforation of the vessels with the formation of the restricted and pulsating hematomas, oftentimes with preserved distal circulation. The characteristic feature is that the small fragments were often resulting in the so-called "mine-like" wounds with the complex and irregularly-shaped wound channels, causing the combined injuries of veins and arteries. The discrepancy between the small entry hole and the vast inner damage of the soft tissues and the bones was reported in 75% of such wounds, which required the obligatory conduct of ultrasonic dopplerography, and in the complex cases — the computed tomographic angiography with contrast enhancement (CT-angiography), with obligatory thorough revision of the wound channel.

The medium size fragments — 1–3 cm (in 37% of the operated individuals) — were causing the variable damage: from the marginal defects to the complete transverse ruptures of the vessels. The specific feature of such wounds was the frequent combination with the damage of the adjacent nerve trunks. Large fragments — sized over 3 cm (14% of the operated) — were causing the extensive damage with vast defects of the vascular walls and with the massive tissue destruction. Such wounds were characterized by the formation of the vast zones of tissue contusion, by the high risk of secondary thrombosis and by the necessity of vast surgical processing.

The type and the number of conducted surgeries in the patients enlisted into the research are provided in table 2.

At the earliest post-surgery period (first two days) the post-ischemic syndrome has caused the need for extracorporal detoxication in 5 (9%) wounded, the secondary amputation of the lower limb was done only in one (1.8%) operated patient in 9 hours from the initial surgery. No cases of lethal outcome were reported among all the operated patients (0%).

The multiplicity of the manifestations of the battle-inflicted trauma of the major vessels in the limbs is better to be demonstrated by the description of several clinical examples.

Clinical case description

Clinical example 1. To the Admission Ward, the 32-year old patient was admitted 6 hours after the mine-blast injury of the left shoulder. At the pre-hospital phase, the medical team has carried out the temporary bypassing of the brachial artery using the sterile plastic tube.

On admission, the status of the patient was considered stable with moderate degree of severity, with satisfactory blood supply in the distal areas of the limb and with the absence of signs of acute ischemia. The patient had a tear-contused wound with the size of 3.0×2.5 cm in the middle third of the left shoulder with insignificant blood discharge. The observed findings included the defect in the brachial artery with a length of up to 4 cm, replaced with temporary shunt. The pulsation in the peripheral arteries was preserved, though weakened. The neurological status remained intact: the sensitivity and the ability to move the palm and the fingers was completely preserved. Moderate swelling was found in the soft tissues in the damaged area. The instrumental diagnostics included the DUS of the vessels, on the results of which, signs of distal

Table 2

Types of surgeries

Wound location	Type of surgical intervention	Patients *n*=57 (%)
Upper limb *n*=21, 37%	Resection of the artery with autovenous prosthetic replacement using the reversed segment of *v. saphena magna* or *v. basilica*	16 (28)
	Circular resection of the artery with direct anastomosis	5 (9)
Lower limb *n*=36, 63%	Resection of the artery with autovenous prosthetic replacement using the reversed segment of *v. saphena magna* or *v. basilica*	33 (58)
	Circular resection of the artery with direct anastomosis	3 (5)
	Fasciotomy	29 (51)

hypoperfusion were found with persisting passability in the temporary shunt. The radiology examination has shown the presence of the radiopaque foreign body of irregular shape with the size of 2.0×1.5 cm within the soft tissues of the medial surface of the shoulder. No other injuries were revealed in the patient.

In the settings of the endotracheal anesthesia, the surgical intervention was done at the extent of the primary wound processing, the revision of the wound channel and the removal of the damaging fragment. Upon the revision, it was found that there is a segmental defect in the brachial artery with a length of 4 cm with crushed vessel ends. Resection of the damaged segment was done with further autovenous prosthetic replacement using the reversed transplant made of the great saphenous vein, extracted from the right thigh (Fig. 1). The vascular reconstruction was carried out using the microsurgery technique and the suturing material was the prolene 7/0. The surgery was completed with using the wound draining and the layered suturing.

The postoperative period was unremarkable (no complications). The control ultrasound examination has confirmed the complete passability of the reconstructed segment of the artery and the restoration of the magistral circulation. Other findings included the restoration of the full-fledged pulsation in the peripheral arteries. The status of the patient was deemed stable and he was evacuated for further treatment to the specialized institution in the rear areas.

Later on, during the after-treatment in another institution, his postoperative period was still unremarkable (no complications). The control DUS has confirmed the complete passability of the reconstructed arterial segment with preserving the magistral circulation.

This observation demonstrates the successful application of the two-staged treatment tactics for the major artery injury, including the temporary bypassing at the pre-hospital phase and further autovenous prosthetic replacement at the in-patient settings. The timely conducted vascular reconstruction allowed to prevent the development of ischemic complications and to salvage the limb, which emphasizes the importance of the continuity at the stages of providing the medical aid.

Clinical example 2. To the admission ward, a 28 years old patient was transported 2 hours after the multiple fragmentation wound of the right lower limb. The wound in the popliteal area was characterized as the non-perforating with supposed injury of the vascular bundle elements. The status of the patient on admission remained stable with compensated hemodynamic parameters and with the absence of clinical signs of acute ischemia in the limb.

Upon the local examination, in popliteal fossa, the visualized finding included a wound with a diameter of 2 cm with insignificant hemorrhage. The pulsation in the peripheral arteries of the foot was detectable but weakened. The sensitivity and the motor function in the distal areas of the limb were completely preserved. Moderate edema was found in the perivascular tissues.

The results of the DUS have revealed signs of combined injury of the popliteal artery and vein with the formation of limited hematoma. The blood supply in the distal areas of the limb was preserved. The radiology examination has confirmed the presence of the radiopaque fragment of irregular shape within the soft tissues of the popliteal region.

In the settings of the endotracheal anesthesia, a surgical intervention was carried out at the extent of

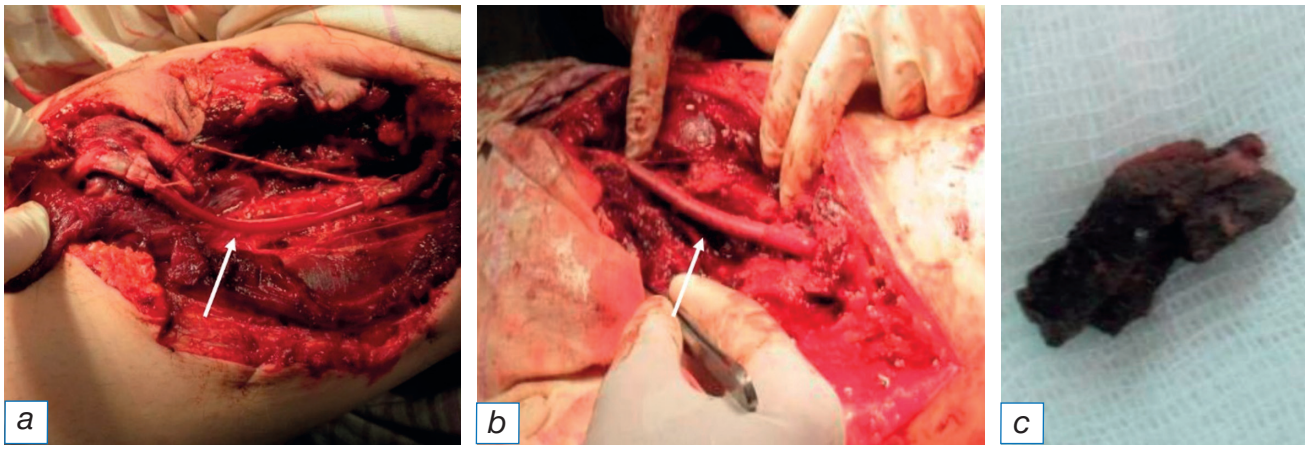

Fig. 1. Resection of the damaged segment. *a* — temporary shunting of the brachial artery (arrow); *b* — replacing the defect of the brachial artery with reversed auto-vein (arrow); *c* — removed shell fragment.

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the revision of the wound channel, the removal of the fragment, the reconstruction of the artery and suturing of the vein defect. Intraoperatively, the marginal defects were found in the popliteal artery and vein with a length of up to 1.5 cm. Further procedures included the resection of the damaged areas of the popliteal artery with further autovenous prosthetic replacement using the reversed transplant made of the great saphenous vein. The vascular reconstruction was done using the microsurgery technique (Fig. 2).

The postoperative period was characterized by the complete restoration of the blood supply in the limb. The control ultrasound examination has confirmed the passability of the reconstructed vessels. The patient was mobilized on the next day and evacuated for further treatment.

The specific features of this observation were the combined injury of the popliteal artery and vein, the optimal timings of the evacuation after the injury and the absence of significant ischemia, which has specifically defined the possibility of conducting the primary vascular reconstruction with favorable prognosis in terms of the recovery.

Clinical example 3. The patient aged 35 years was transported to the Admission Ward 3 hours after receiving a non-perforating bullet wound in the soft tissues of the right shin. The status of the patient on admission was evaluated as severe due to the on-going hemorrhage out of the wound channel. At the pre-hospital phase of providing the medical aid, a tourniquet was applied above the wound location — to the upper third of the right thigh.

On admission, the characteristic signs of hemorrhagic shock were observed: pronounced paleness of the skin, cold sweat, tachycardia up to 120 bpm and arterial hypotension (80/50 mm.Hg.). The local status was described as the presence of arterial tourniquet at the upper third of thigh and a wound hole with diameter of 1.5 cm in the middle third of the shin with signs of on-going venous hemorrhage. No pulsation was found in the peripheral arteries of the foot due to the tourniquet applied.

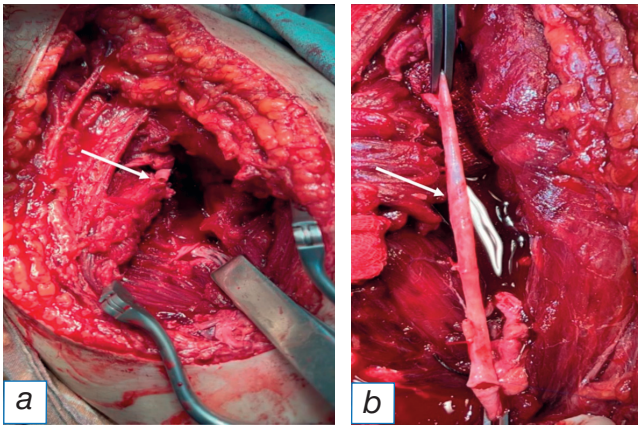

Fig. 2. Resection of the damaged areas of the popliteal artery. *a* — the defect of the popliteal artery (arrow); *b* — the prosthetic replacement of the popliteal artery with reversed auto-vein (arrow).

An emergency ultrasound examination has revealed the damage of the great saphenous vein with preserved magistral arterial vessels. The radiography has confirmed the presence of a foreign body (bullet) within the soft tissues on the posterior surface of the shin. The laboratory tests have shown the critical decrease in the levels of hemoglobin — down to 78 g/l and hematocrit — down to 24%.

During the emergency surgical intervention, an immediate removal of the arterial tourniquet was done with further revision of the wound channel. Intraoperatively, a defect was found in the wall of the great saphenous vein with a diameter 1.0 cm. The defect was fixed by means of applying the vascular suture with prolene 6/0 suturing material (Fig. 3). The complete arrest of hemorrhage was achieved immediately. For the correction of the hemorrhagic shock, the hemotransfusion was done using 500 ml of erythrocyte concentrate and 600 ml of fresh frozen plasma.

The postoperative period was characterized by the rapid stabilization of hemodynamic parameters and by the restoration of the peripheral blood circulation parameters. The control ultrasound examination has confirmed the maintained passability of the reconstructed vein.

This clinical observation decisively demonstrates the iatrogenic complication expressed as the erroneous application of the tourniquet above the wound location in case of venous bleeding, which lead to the aggravation of the blood loss and to the development of severe hemorrhagic shock. The special complexity was observed in the differential diagnostics of the type of hemorrhage with the atypical trajectory of the wound channel.

Clinical example 4. A 31-yeal old patient was admitted to the in-patient hospital in 3 hours after receiving a fragmentation wound in his left thigh. At the pre-hospital phase, a tourniquet was applied at the level of the thigh, however, its application did not provide an adequate hemostasis. The status of the patient on admission was considered extremely severe due to the voluminous venous hemorrhage and due to the developed hemorrhagic shock.

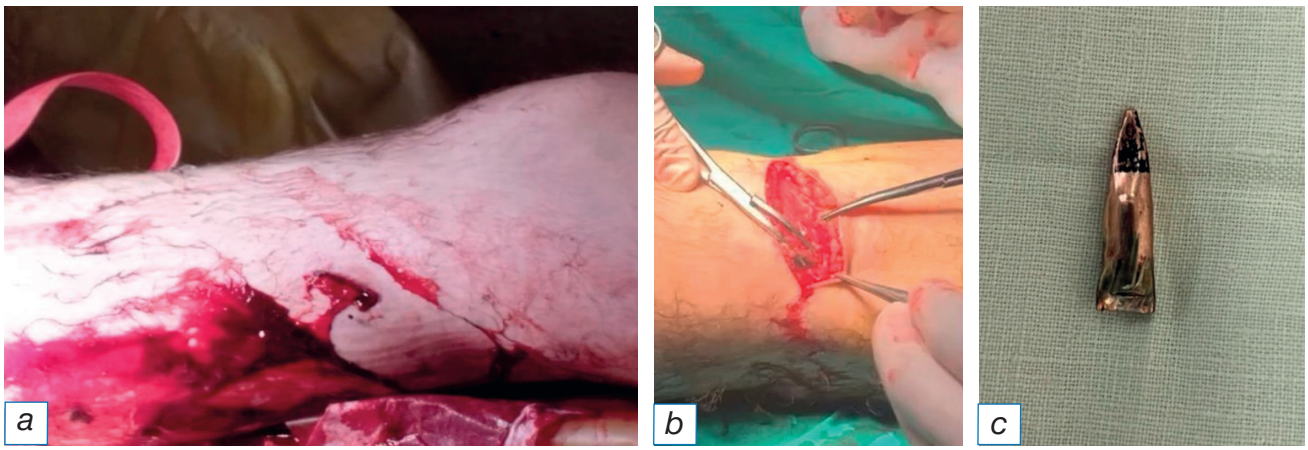

Fig. 3. Elimination of a defect in the wall of the large saphenous vein. *a* — the appearance of the wound; *b* — suturing the defect of the great saphenous vein; *c* — bullet extracted from the wound.

Upon the surgical revision, the findings include the damage of the femoral bone in the lower third with secondary injury of the popliteal vein with bone fragments. The removal of the tourniquet was done with further applying the vascular suture to the damaged area of the vein. Restoring the vessel integrity has allowed for achieving a complete hemostasis. The second step included the surgical processing of the bone damage with the repositioning and fixation of the bone fragments. The postoperative period was characterized by the stabilization of hemodynamic parameters and by the restoration of an adequate venous outflow in the limb.

This observation shows the specific features of the tactics in cases of combined injuries of the bone tissue structures and of the major venous vessels. It also emphasizes the importance of the staged treatment approach, where the principal attention is paid to restoring the vascular passability with further stabilization of the fractured bone fragments (Fig. 4).

The clinical observations 3 and 4, though not being directly related to the injuries of the arteries, demonstrate the major importance of the differential diagnostics between the arterial and the venous hemorrhages at the pre-hospital phase, as well as the necessity of controlling the arrest of hemorrhage after the application of the tourniquet for the purpose of ruling out the cases of incorrect first medical aid for venous bleeding.

Clinical example 5. A 22-years old patient was transported to the Admission Ward with a mine-blast wound of the left shoulder with unknown exact timings of the wound. Upon the initial assessment, there was an absence of pulse in the radial artery, the absence of active motions in the elbow and in the radiocarpal joints with the absence of tactile sensitivity in the affected limb, however, the passive motions in the joints were preserved. During the intraoperative revision, the findings included a lengthy thrombosed segment of the brachial artery with the delamination of intima and with signs of contusion damage and rupture of the vascular wall. A decision was drawn up on conducting the thrombectomy with further resection of the damaged area of the artery. The vascular defect was replaced

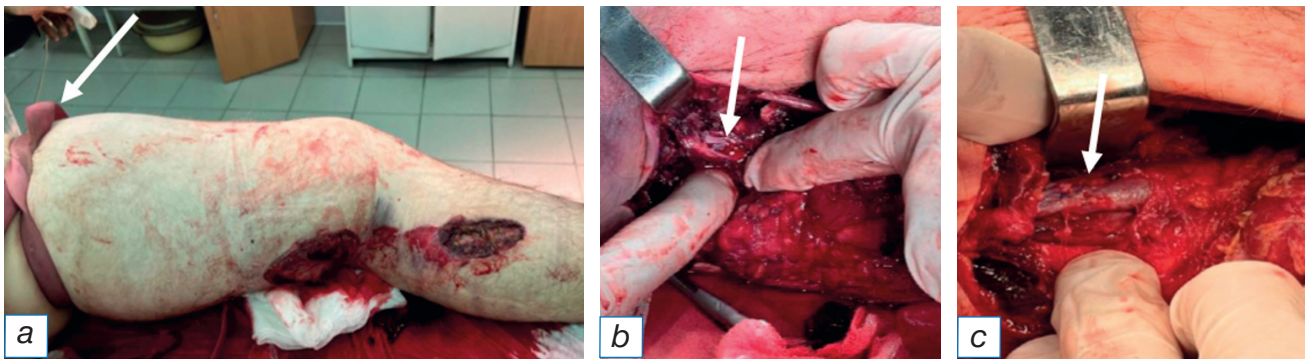

Fig. 4. Restoring the vascular passability. *a* — the appearance of the wound in the left lower limb, tourniquet applied to the upper third of thigh (arrow); *b* — the defect of the popliteal vein (arrow); *c* — suturing the defect in the popliteal vein (arrow).

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with the autovenous transplant made of the great saphenous vein (Fig. 5).

After restoring the magistral circulation, the gradual improvement was observed in the perfusion of the distal areas of the limb. At the remote period, the complete restoration of the limb functions was achieved.

This observation confirms the efficiency of re-vascularisation even in case of visible signs of severe acute ischemia. The maintained passive mobility of the joints has served as the key prognostic sign determining the success of the reconstructive intervention.

Clinical example 6. After a total of 8 hours after the fragmentation wound, into the admission ward, the patient was transported, aged 48 years and with the isolated injury of the femoral artery, complicated by the development of the tense hematoma and with the clinical signs of acute uncompensated ischemia in the limb. Upon the initial assessment, there were characteristic signs of critical impairment of peripheral circulation: marbling of the skin, absence of capillary refill or distal pulse, impaired active motions and sensitivity in the lower limb. The passive motions in the ankle joint of the affected limb were preserved.

In the settings of the operating room, an emergency surgical processing of the wound channel was carried out with the revision of the damaged area. Intraoperatively, a segmental defect of the femoral artery was diagnosed, requiring its resection. The restoration of the arterial continuity was achieved by means of the autovenous prosthetic replacement using the reversed transplant originating from the great saphenous vein.

The specific feature of the surgical tactics was conducting the fasciotomy aimed at preventing the development of the compartment-syndrome after restoring the magistral circulation. The direct result of the intervention became the complete re-vascularisation of the limb with restoring the pulse at the operating table (Fig. 6).

During the postoperative period, gradual regress of ischemic manifestations was observed with the complete restoration of the limb functions. The control ultrasonic examinations have confirmed the persisting passability of the reconstructed arterial segment.

In this observation, despite the significant temporal delay of the admission, the consecutive procedures of surgical processing, the vascular reconstruction and the fasciotomy has allowed for achieving the favorable outcome. The case demonstrates the efficiency of using the autovenous stenting in the settings of the delayed provision of the specialized medical aid.

Clinical example 7. Four hours after the fragmentation wound of the shoulder area, to the in-patient hospital, the patient aged 21 years was admitted with the combined injury of the brachial artery and of the median nerve. Upon the initial assessment, the findings included the preserving of the passive mobility in the limb with the complete absence of peripheral pulse, of the active motions or the tactile sensitivity in the limb.

The intraoperative revision has shown a lengthy segmental defect in the brachial artery with a length of 4 cm along with the complete trans-section of the median nerve at the same distance. A decision was drawn up on conducting the simultaneous reconstructive intervention.

At the first stage, the autovenous prosthetic replacement of the brachial artery was done using the reversed transplant from the *v. basilica*. After the restoration of the magistral circulation, the second stage surgery was carried out — replacing the defect of the median nerve with the autotransplant of the sural nerve (*nervus suralis*) taken from the area of the medial malleolus.

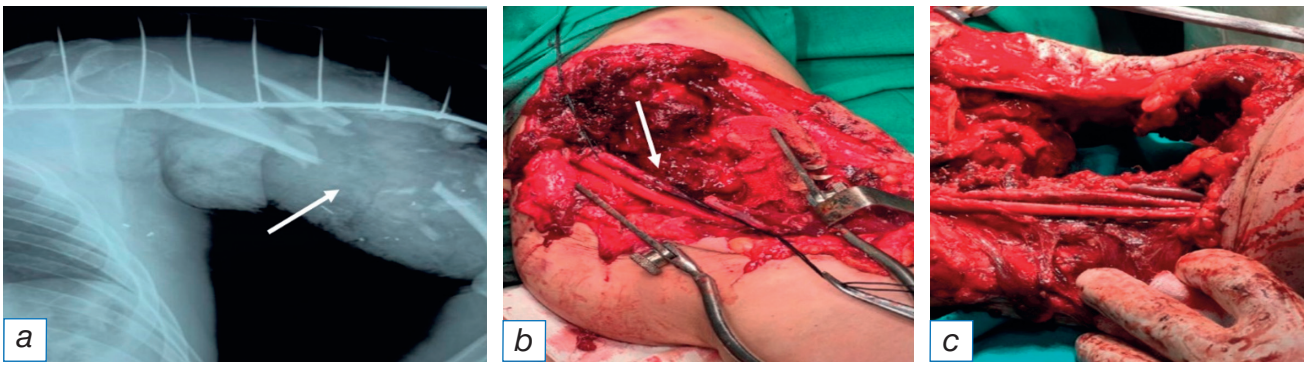

Fig. 5. The vascular defect was replaced with the autovenous transplant. *a* — radiography of the left shoulder (destruction of the humeral bone shown by the arrow); *b* — the defect of the brachial artery in the left shoulder (arrow); *c* — autovenous prosthetic replacement of the left brachial artery.

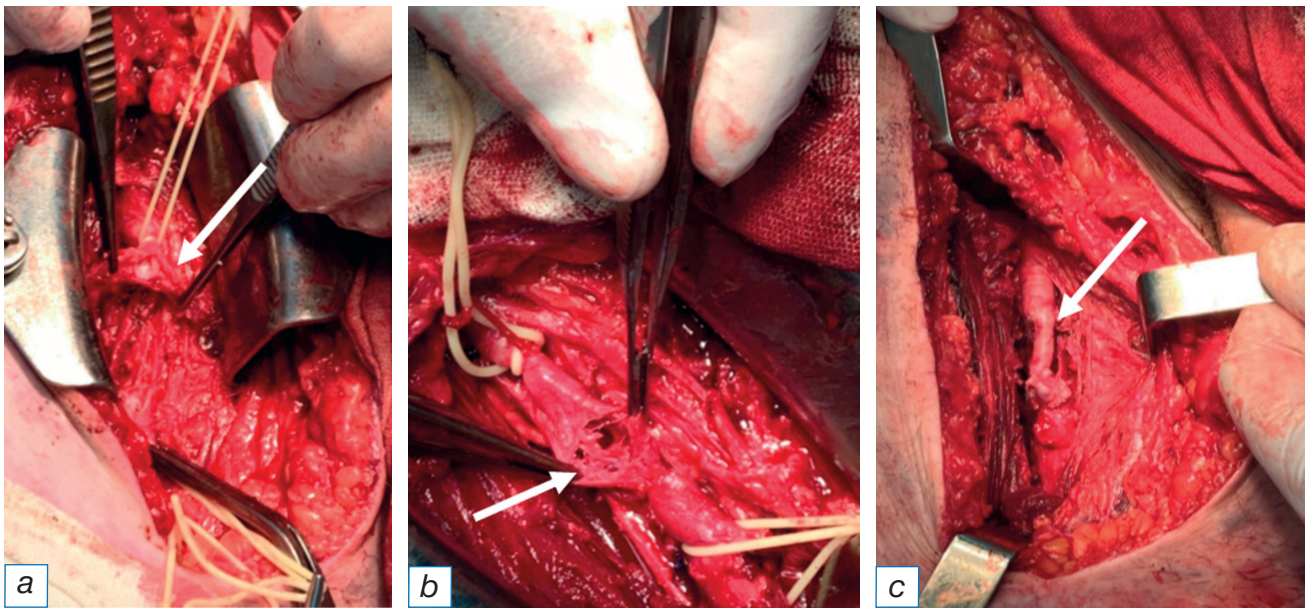

Fig. 6. Performing a fasciotomy. *a, b* — the defect of the femoral artery (arrows); *c* — autovenous prosthetic replacement of the femoral artery (arrow).

The postoperative period was characterized by the gradual restoration of the peripheral circulation and by the initial signs of re-innervation. Later on, the patient was reporting the progressing re-gaining of the motor and the sensory functions in the limb (Fig. 7).

This observation illustrates the possibilities of conducting the complex reconstructive interventions in the settings of the near-front line in-patient hospital. The absence of ischemic contracture has defined the possibility of arranging the simultaneous neurovascular reconstruction. The case demonstrates the importance of the combined approach in restoring not only the anatomical integrity, but also the functional substantiality of the damaged limb.

Clinical example 8. The patient aged 41 was transported to the Admission Ward 4 hours after receiving a fragmentation wound in his right axillary area. The status of the patient on admission was considered as moderate degree of severity, however, despite the relative stability of hemodynamic parameters, progressing paleness was reported in the skin along with increasing fatigue.

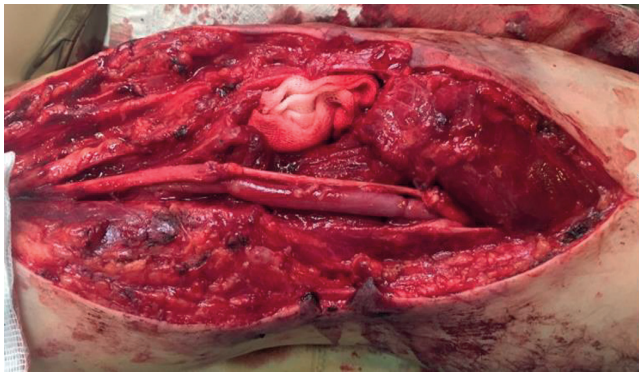

Fig. 7. Autovenous prosthetic replacement of the brachial artery using the reversed transplant from the *v. basilica*.

Upon the clinical examination, in the area of the right axillary fossa, the visualized findings were the tense hematoma with a diameter of approximately 8×10 cm and with pronounced pulsation. The peripheral pulsation in the arteries of the forearm and of the palm was not found. Other signs included the decrease in the dermal sensitivity along the medial surface of the shoulder and of the forearm.

The emergency computed tomographic angiography with contrast enhancement has revealed the complete rupture of the axillary artery at a length of 3 cm with forming the vast pulsating hematoma.

In the settings of the operating room and under the endotracheal anesthesia, the surgical intervention was carried out. After opening and evacuating the hematoma, a segmental defect of the axillary artery was found with a length of 4 cm and with shattered margins. Further procedures included the resection of damaged area with further autovenous prosthetic replacement using the reversed transplant made of the great saphenous vein. The vascular suture was applied using the microsurgery technique. Intraoperatively, the restoration of the pulse in the peripheral arteries was reported (Fig. 8).

The postoperative period was characterized by the gradual restoration of the blood supply in the limb. The control ultrasound examination has confirmed

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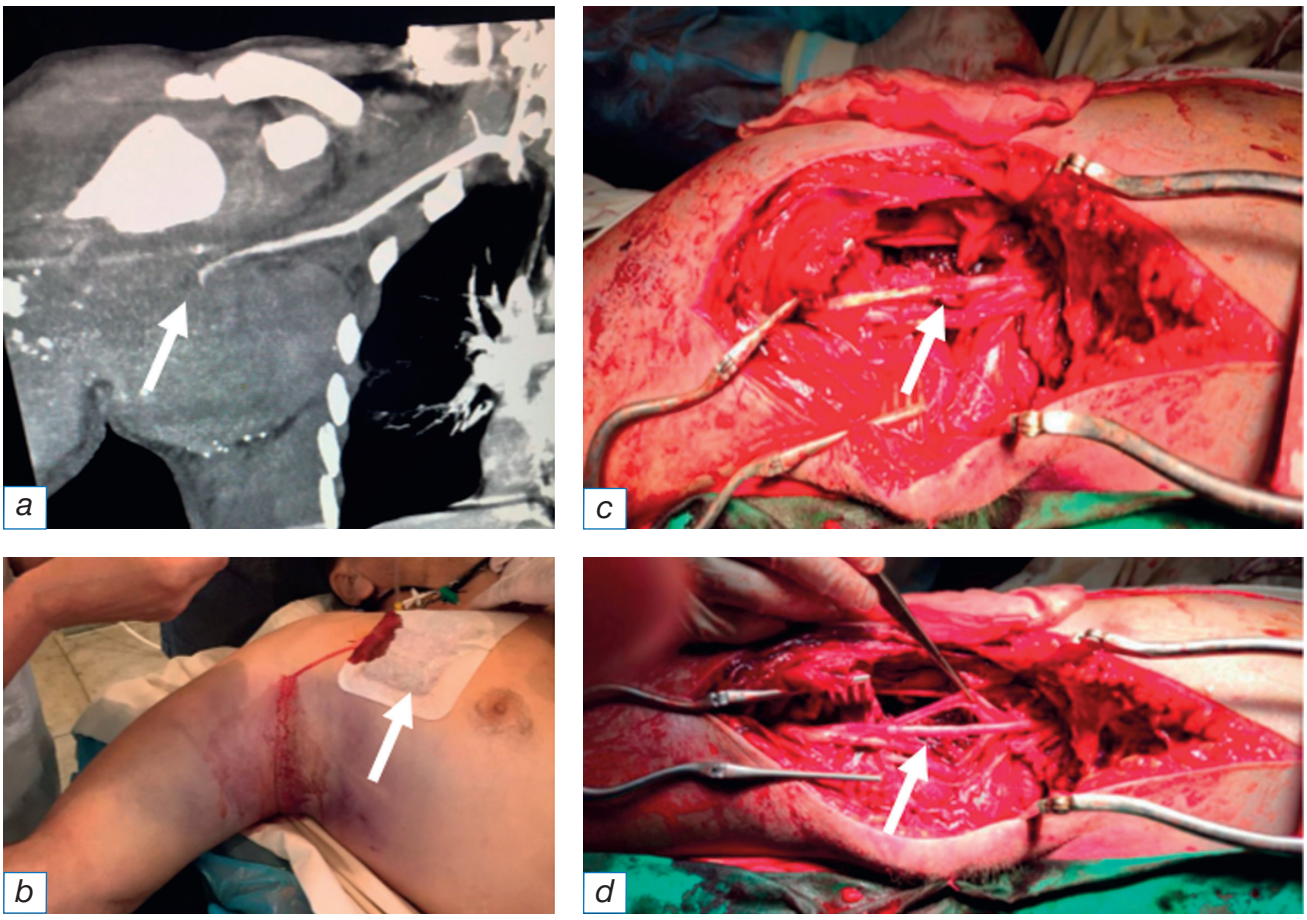

Fig. 8. The restoration of the pulse in the peripheral arteries. *a* — the computed tomographic angiography demonstrating the defect in the right axillary artery with the formation of the pseudo-aneurism and the thrombosis (arrow); *b* — the appearance of the wounded (the entry hole is marked with an arrow); *c* — the defect of the axillary artery (arrow); *d* — the prosthetic replacement of the axillary artery with reversed auto-vein (the autograft is marked by the arrow).

the complete passability of the reconstructed arterial segment. Progressive restoration was reported in the sensitivity and in the motor functions of the limb.

The presented observation demonstrates the successful usage of CT-angiography for the precise local diagnostics of the complex proximal injury of the major vessel. The timely conduct of the autovenous prosthetic replacement has allowed for not only salvaging the limb, but also for restoring its full functionality, despite the initially severe type of injury and the developing ischemia. The case confirms the necessity of the possibility to perform the emergency CT-angiography in the settings of the multi-profile in-patient hospital at the near-front line territory.

DISCUSSION

Within the framework of the current research, a retrospective analysis was arranged for the clinical observations of the modern battle injuries of the magistral arteries in the limbs. The number of wounded admitted with such injuries is significantly higher comparing to the experience from the previous conflicts (for example, during the Great Patriotic War, the vessel wounds were described in 1% of the wounded, and during the Chechen conflict — in 5–6%, we were registering the vessel injuries in 18% of the admitted wounded patients) [1–4]. Some role in this statistics, probably, is played by the improvement in the provision of first medical aid at the battlefield, but the main reason is the usage of new types of weaponry (cluster munitions and other types of modern shells). The combined nature of the wounds, which we observed, requires the participation of the multidisciplinary team of specialists (orthopedic traumatologist, vascular surgery specialist, neurosurgery specialist, abdominal and thoracic surgery specialist, anesthesiologist-intensivist and specialists from the diagnostic fields).

The diagnostics of the injured arteries of the limbs can pose difficulties when the input hole of the damaging element is located outside the projection of the vessel location area and there is no arterial hemorrhage. Our experience confirms the key role of ultrasonic

dopplerography, while the CT-angiography conducted in the setting of the stable hemodynamics provides the unique possibilities for the pre-operative planning in the complex situations, especially when there are multiple fragment wounds and the determination of the damage level is hampered.

In cases of the injured major vessels of the limbs, oftentimes there is a significant degree of destruction of the tissues along with the corrugated wound channels and with the contusion damage, which does not allow for objectively evaluating the sensitivity, the active motions and the degree of ischemia at the same time. During the research, it became clear that the specific features of the effects of damaging elements in the modern conflict lead to the absence of the absolute criteria for the development of the irreversible limb ischemia (including the time of injury, the pulsation, the ultrasonic dopplerography data, the absence of sensitivity and muscle rigidity), except for the development of ischemic contractures in the major joints.

The time of wound infliction was traditionally considered a significant factor for the development of irreversible ischemia, however, there is a whole number of reports, in which, using their own experience, the authors did not find any confirmation to this. S.R. Menakuru et al. [5], describing a series of 148 patients, report about the excellent results, despite the median delay of 9.3 hours from the moment of the admission of the wounded. W.H. Wagner et al. [6] have found no correlation between the ischemia time and the outcome in vascular injury. W. de Silva et al. [7] describe the brilliant results for 36 vascular reconstructions with the median time from the episode of injury being 10 hours. In our practice, in a number of patients, the successful vascular reconstructions were undertaken after more than 24 hours from the moment of the wound infliction.

The analysis of the accessible literature shows that it is possible to use the tactics of restoring all the major vessels regardless of the degree of ischemia in the limb. Even in the absence of restoring the peripheral blood supply in the limb, it is possible to delay the conduct of the secondary amputation, for the ischemia can be mosaic and the staged necrectomies with a background of using the extracorporeal methods of detoxication allow for salvaging the limb [4–7]. However, the use of this approach requires significant efforts from the medical staff, the proper equipment basis and the continuity in the settings of the staged provision of medical aid.

In each case, the decision on the possibility of conducting the vascular reconstruction needs to be drawn up on an individual basis. It should be remembered that the main objective of the medical aid in the settings of the military conflict is saving the life of the maximum number wounded in case of their massive inflow. The choice of the general strategy of treatment at the stage of the sorting decision should be based on evaluating the vital functions (consciousness, hemodynamics, respiration) and on the presence of the "triad of death" (hypothermia, acidosis, coagulopathy). In the unstable patients with severe combined injuries, a fast and reliable arrest of the on-going hemorrhage is needed, while the surgical tactics should be based on the practicability principles.

We have developed a proprietary algorithm of selecting the treatment tactics (Fig. 9), which we used as a guideline during our operations and which has confirmed its high clinical efficiency. Three variants of the tactical surgical decision are possible: the vascular

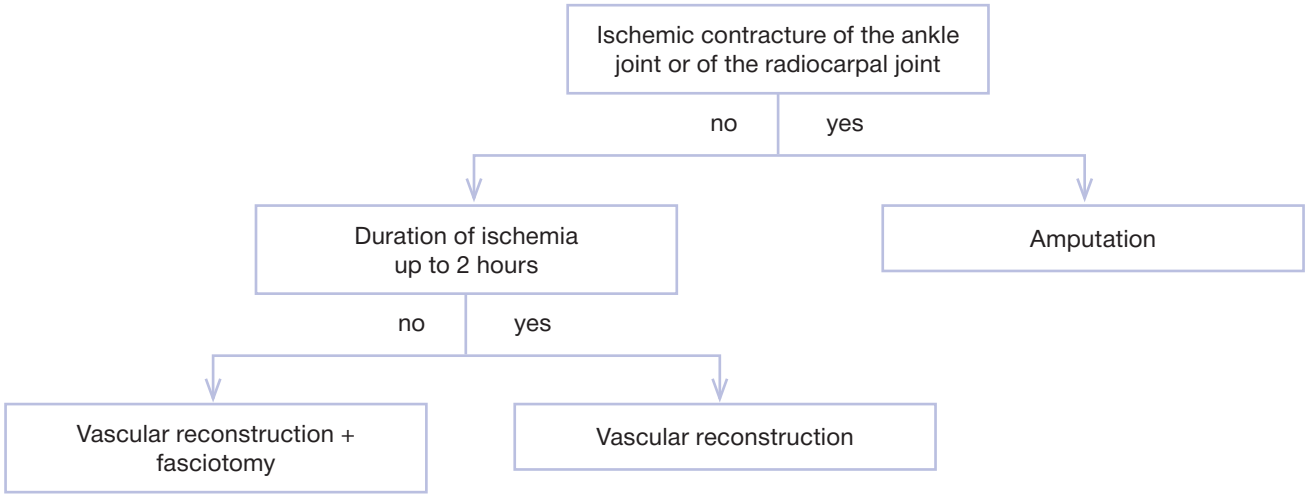

Fig. 9. The algorithm of selecting the treatment tactics in cases of injuries involving the magistral arteries of the limbs.

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reconstruction, the vascular reconstruction together with fasciotomy and, finally, the amputation. Special significance when selecting the specific variant belongs to evaluating the passive movements in the damaged limb in its major joints as the more reliable prognostic criterion of its viability. The absence of active motions and of the sensitivity are reversible, besides, they can occur in cases of the concomitant damage of the nerves, not being an indication for amputation.

In cases of the damaged arteries of the lower limb, only in an ideal situation, when the wound was inflicted less than 2 hours ago and there is no significant destruction of the tissues, it is possible to skip the fasciotomy. In other cases, fasciotomy is indicated, and skipping it may further lead to the compartment syndrome and to the acute renal insufficiency. Though the necessity of fasciotomy is evident when detecting signs of swelling and pain in the distal muscles, it may not be the case when we are talking about the prevention [8, 9]. It was shown that early fasciotomy in cases of damaged vessels in the lower limbs promotes to the decrease of the rates of consequent amputations and to the shortening in the duration of treatment [10]. Fasciotomy for preventive purposes in case of acute ischemia in the upper limb can be unjustified. Thus, in the research by D. Jo et al. [11] performing the fasciotomy had no evident benefits and was associated with the increased rate of complications. In our research, in cases of traumas involving the vessels of the upper limb, the fasciotomy was not performed on the routine basis.

With the concomitant damage of the bones, the majority of orthopedic fixations were the external ones and, with the traumatologist having the sufficient experience, they were done rapidly and in parallel to the operations conducted by the vascular surgery specialist. There were no staging problems and the majority of vascular anastomoses were conducted in the already stabilized limb. In rare cases, when the traumatologists needed significant time for the fixation of the limb, the restoration of the passability of the arteries was done as the first stage.

During the postoperative period, the observed findings may include the progression of ischemia and the development of the acute renal insufficiency, which will require the immediate response measures (secondary amputation and/or extracorporal detoxication) (Fig. 10). We suggest that, after conducting the vascular reconstructions, the active follow-up is necessary within two days, and the premature evacuation of the patient can increase the risks caused by the untimely provision of the adequate medical aid.

The complex operative situation and the possibility of safe evacuation of the wounded and the injured can significantly modify the application of the classic concept of “multi-stage” treatment, which dictates the necessity of developing the flexible and adaptive protocols for evacuation and treatment.

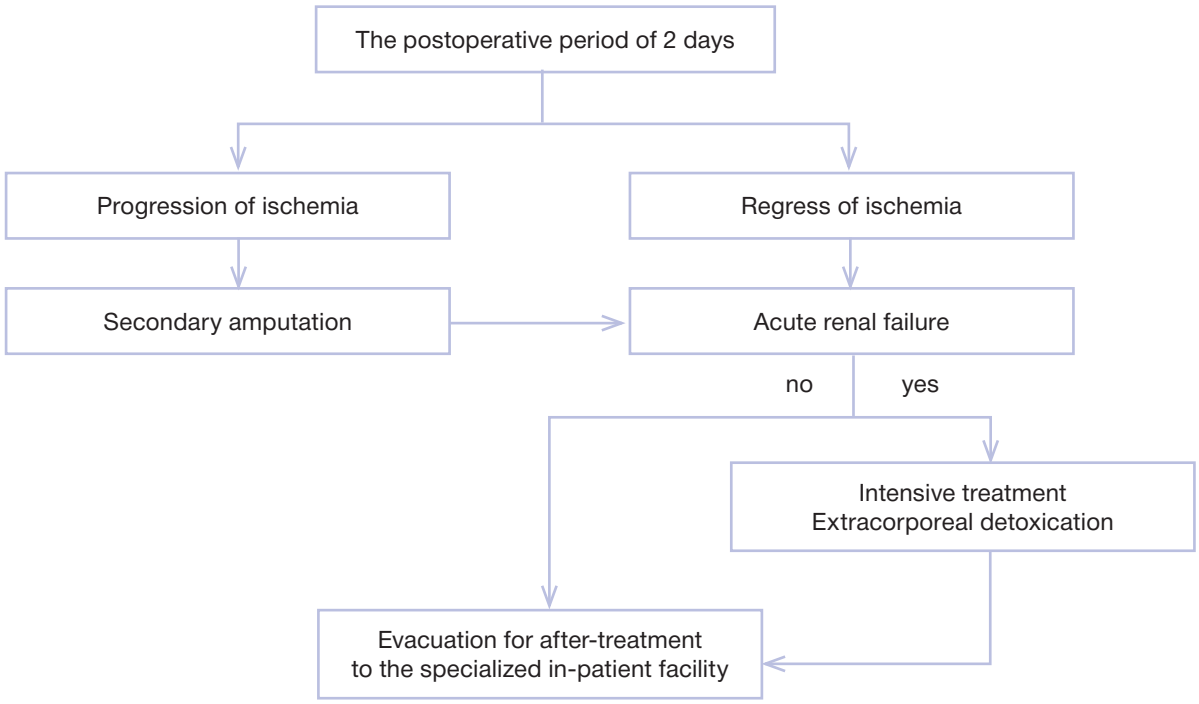

Fig. 10. Algorithm of managing the patient after the restoration of the magistral arteries in the limb.

Our experience demonstrates the high level of qualification among the front-line medical groups, which, in the settings of being at the zone with immediate danger, were conducting such surgical interventions as the temporary bypassing of the damaged blood vessels, which was providing the possibility of salvaging the limb. At the same time, a systemic risk was identified for the application of the arterial tourniquet in cases of isolated venous bleeding, which indicates the necessity of perfecting the educational programs of pre-hospital aid with an accent to the differential diagnostics of the hemorrhage type.

In the settings of the well-equipped civilian in-patient hospitals located near the areas of the military operations, it is possible to arrange the vascular reconstructive surgeries in cases of the injuries of the magistral arteries, however, due to the risk of developing the post-ischemic syndrome, it is practicable to avoid the immediate further evacuation and to arrange the follow-up for the operated patients lasting not less than two days (see Fig. 10). Due to the absence of direct contacts between the institutions providing medical aid at various stages, the continuity can be interrupted, which negatively affects the final result of treating the wounded.

CONCLUSION

In the settings of the modern battle conflict, a combination can be observed that includes the unique characteristic of the wounds and the complex operating environment, which requires the exceptional coordination of the forces and facilities when organizing the medical aid and defines the necessity of individual tactical decision in each specific patient. The battle contact line can be located at the direct proximity from the well-equipped civilian healthcare institutions, at the premises of which, it is possible to provide the high-tech medical aid, however, in case of performing the complex surgeries, the follow-up for the operated patient at the earliest post-surgery period is practicable for arranging on site with avoiding the immediate evacuation.

In cases of injuries involving the major artery in the limb, the main parameter affecting the possibility of salvaging the limb itself is the degree of ischemia in the muscles. The irreversible ischemia is often hard to define, and the guideline to be used is the development of the ischemic contracture in the major joints. The time of wound infliction, the absence of pulse, of the active motions and of sensitivity cannot serve as an indication for amputation. The algorithm developed by us has demonstrated its high efficiency in saving the life and in salvaging the limb.

ADDITIONAL INFORMATION

Author contributions: *A.V. Smirnov*, *R.I. Khabazov*, *S.V. Deryabin*, general concept, collection and analysis of material, writing the article, editing; *S.V. Deryabin*, *M.V. Khruslov*, *P.Yu. Orekhov*, *P.Yu. Parshin*, *A.R. Abasov*, execution of operations; *A.V. Troitskiy*, general concept, general management. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval: The study was approved by the local ethics committee of the Federal Scientific and Clinical Center of the Federal Medical and Biological Agency of Russia (protocol No. 9/2025 dated Sept 15, 2025). All patients included in the study signed informed voluntary consent for treatment and surgery, as well as for the use of anonymized health data for scientific purposes.

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Statement of originality: The authors did not utilize previously published information (text, illustrations, data) in conducting the research and creating this paper.

Data availability statement: The editorial policy regarding data sharing does not apply to this work, data can be published as open access.

Generative AI: Generative AI technologies were not used for this article creation.

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Risk Factors for Post-Operative Cognitive Dysfunction in Neurosurgical Patients

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ABSTRACT

BACKGROUND: *The impact of various risk factors on the development of post-operative cognitive dysfunction in neurosurgical patients requires research for decreasing the probability of developing this complication.* ***AIM:*** *To determine the effects of extra- and intraoperative risk factors on the development of post-operative cognitive dysfunction in neurosurgical patients after undergoing a vertebral column surgery with long-running anesthetic support.* ***METHODS:*** *The research was carried out among the neurosurgical patients with previous surgical intervention in the vertebral column, within the premises of the Neurosurgery Department of the State Budgetary Healthcare Institution of the Tyumen Oblast "Regional Clinical Hospital No. 2". The evaluation included the cognitive functions before surgery and on Day 3 after the surgical intervention using the Montreal Cognitive Assessment (MoCA), along with a panel of Isaac tests and the Munsterberg test. The calculated coefficients were the Pearson's and the point biserial correlation coefficients regarding the following intraoperative risk factors: type and duration of anesthetic management, medications used for anesthesia and muscle relaxation, as well as the type of surgery. Evaluations were also made for the interrelation between the development of post-operative cognitive dysfunction and the following extra-operational risk factors: the age, the body mass index, the number of education years, the presence of arterial hypertension or diabetes and smoking.* ***RESULTS:*** *A notable positive correlation was observed between the development of post-operative cognitive dysfunction and the age ($r=0.53$; $p<0.01$), moderate correlation with the body mass index ($r=0.35$; $p<0.01$) and with the presence of arterial hypertension ($r=0.42$; $p<0.05$). A moderate negative relation was observed for the number of education years and the development of post-operative cognitive dysfunction ($r=-0.36$; $p<0.01$). The relation of the presence of diabetes with post-operative cognitive dysfunction did not show significant correlation. Smoking and surgery duration show low level of interrelation, which does not allow to comprehensively interpret the obtained results as significant. The type of surgical intervention and the duration of anesthetic support did not correlate with the development of post-operative cognitive dysfunction ($r<0.1$; $p<0.01$). A moderate correlation was found for the anesthesia conducting using a drug combination of desflurane+fentanyl ($r=0.31$; $p<0.05$) along with the mild one when combining sevoflurane+fentanyl+ketamine ($r=0.25$; $p<0.05$). The usage of fentanyl together with sevoflurane ($r=0.07$), propofol ($r=-0.1$) and sodium oxybutyrate ($r=0.05$) does not lead to post-operative cognitive dysfunction ($p<0.05$).* ***CONCLUSION:*** *Elderly age, high body mass index, presence of arterial hypertension and low education level increase the risks of developing post-operative cognitive dysfunction. Using the desflurane+fentanyl and sevoflurane+fentanyl+ketamine combinations can also contribute to the occurrence of cognitive disorders.*

Keywords: *post-surgery cognitive dysfunction; long-running anesthesiology support; risk factors.*

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BACKGROUND

Post-operative cognitive dysfunction (POCD) is a state which is quite often diagnosed in patients undergoing long-running surgical intervention. POCD is described as impaired attention concentration, memory, speech, learning ability and other higher mental functions [1]. Such a condition can persist for many months and progress into a constant disorder, seriously affecting the quality of the patients' life and their working capacity. To a great extent, the

Факторы риска послеоперационной когнитивной дисфункции у больных нейрохирургического профиля

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АННОТАЦИЯ

Обоснование. *Влияние различных факторов риска на развитие постоперационной когнитивной дисфункции у пациентов нейрохирургического профиля требует изучения для уменьшения вероятности развития этого осложнения.* ***Цель*** *— определить влияние экстра- и интраоперационных факторов риска на развитие постоперационной когнитивной дисфункции у пациентов нейрохирургического профиля, подвергшихся оперативному вмешательству на позвоночнике при длительном анестезиологическом пособии.* ***Методы.*** *Исследование проводилось среди пациентов, перенёсших операции на позвоночнике, на базе нейрохирургического отделения ГБУЗ ТО ОКБ № 2. Оценку когнитивных функций перед операцией и на третий день после проводили с помощью Монреальской когнитивной шкалы (MoCA), набора тестов Исаака и теста Мюнстерберга. Рассчитывали коэффициенты Пирсона и точечные бисериальные коэффициенты корреляции в отношении следующих интраоперационных факторов риска: вид и продолжительность анестезиологического обеспечения, препараты для анестезии и миорелаксации, вид операции. Оценивали также взаимосвязь между развитием постоперационной когнитивной дисфункции и следующими экстраоперационными факторами риска: возраст; индекс массы тела; число лет обучения; наличие артериальной гипертензии, сахарного диабета; курение.* ***Результаты.*** *Выявлена заметная положительная корреляция между развитием постоперационной когнитивной дисфункции и возрастом ($r=0,53$; $p<0,01$), умеренная корреляция с индексом массы тела ($r=0,35$; $p<0,01$) и наличием артериальной гипертензии ($r=0,42$; $p<0,05$), а также умеренная отрицательная связь с числом лет обучения ($r=-0,36$; $p<0,01$). Связь наличия сахарного диабета с постоперационной когнитивной дисфункцией не имела значимой корреляции. Курение и продолжительность операции имеют низкий уровень связи, что не позволяет полноценно интерпретировать полученные результаты как значимые. Вид оперативного вмешательства и продолжительность анестезиологического пособия не коррелировали с развитием постоперационной когнитивной дисфункции ($r<0,1$; $p<0,01$). Обнаружена умеренная корреляция с использованием в качестве анестезии комбинации препаратов десфлуран+фентанил ($r=0,31$; $p<0,05$) и лёгкая — при сочетании препаратов севофлуран+фентанил+кетамин ($r=0,25$; $p<0,05$). Использование фентанила совместно с севофлураном ($r=0,07$), пропофолом ($r=-0,1$) и натрия оксибутиратом ($r=0,05$) не приводит к постоперационной когнитивной дисфункции ($p<0,05$).* ***Заключение.*** *Пожилой возраст, высокий индекс массы тела, наличие артериальной гипертензии, низкий уровень образования увеличивают риски развития постоперационной когнитивной дисфункции. Применение комбинаций препаратов десфлуран+фентанил и севофлуран+фентанил+кетамин также могут способствовать появлению когнитивных нарушений.*

Ключевые слова: *постоперационная когнитивная дисфункция; длительное анестезиологическое пособие; факторы риска.*

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development of such a set of symptoms depends on certain risk factors [2, 3]. Due to an increase in the number of surgical interventions among the elderly patients, a necessity arises for deeper exploration of such factors. The obtained data allow for providing an individual approach when preparing the patient to surgical intervention and for decreasing the probability of developing POCD by using the means of prevention.

It is known that the occurrence and the severity of POCD vary depending on the presence of pre-operative and intraoperative risk factors, such as the type and the duration of surgery, the type of anesthesia, the age of the patient, the concomitant diseases and the level of education [4–6]. The majority of research works in this field were carried out among the patients of the cardiology and trauma care profile. The research works on the incidence and the severity of POCD in patients having a vertebral column surgery are sparse and concentrated on the influence of the age and the duration of anesthetic support [1, 7]. The analysis of the effects of other risk factors on the cognitive functions among the vertebrology patients will allow for more comprehensive interpreting the results of neuropsychological tests and for preventing the development of POCD.

Research aim — to determine the effects of various extra- and intraoperative risk factors on the development of POCD in neurosurgical patients, undergoing vertebral column surgery with long-running anesthetic support.

METHODS

Research design

Observational selective non-controlled clinical trial.

Conformity criteria

Inclusion criteria: patients with scheduled surgical intervention caused by degenerative-dystrophic diseases of the vertebral column.

Exclusion criteria: patients having ischemic or hemorrhagic stroke in the past medical history; significant blood loss (more than 500 ml); diseases of the nervous system, including the consequences of craniocerebral injuries; alcohol abuse; severe depression; impaired consciousness.

Research facilities

The examination was carried out within the premises of the Neurosurgery Department of the State Budgetary Healthcare Institution of the Tyumen Oblast "Regional Clinical Hospital No. 2" with the participation of a homogeneous group of patients: all of them were neurosurgical patients with long-running (lasting more than 120 minutes) vertebral column surgeries. The research was arranged in the similar settings using the standardized scales, which allowed for maximum increasing the significance of the obtained results.

Research Duration

The research duration was 12 months (from January 2024 until January 2025).

Medical procedure description

The evaluation included the cognitive functions before surgery and on Day 3 after the surgical intervention using the Montreal Cognitive Assessment (MoCA), along with a panel of Isaac tests and the Munsterberg test. For minimizing the practical effect (improvement of parameter values caused by the repeated performing the tests), the second testing employed the parallel versions of tests. The testing was done after evaluating the intensity of pain syndrome using the visual analogue scale. In case of severe pain syndrome, in order to minimize the influence of pain on the testing results, pain treatment was conducted using the non-steroid anti-inflammatory drugs.

Research outcomes

Primary research outcome: the change in the level of cognitive functions in the patients after long-running vertebral column surgeries.

Methods for registration of outcomes

The results of testing and surveying on the paper media were transitioned into the Microsoft Office Excel electronic format for their further statistical processing.

Statistical analysis

For each scale, a difference was calculated between the absolute values of testing results before and after surgery. The obtained parameters were expressed as percentages. The percentages were summed and divided by the number of scales. This approach was used to calculate the mean value of the change (median, Me) for three scales. The mean decrease of the results of three testing sessions by more than 10% was interpreted as the presence of POCD. Calculations were done for the Pearson's coefficients (r) and for the point biserial correlation coefficients regarding the extra-operative (the age; the body mass

index; the number of education years; the presence of arterial hypertension, diabetes and smoking), as well as the intraoperative (drugs used for anesthetic management and for muscle relaxation, duration and type of surgical intervention) risk factors. Correlations were considered statistically significant at the *p* level of ≤0.05. The calculations were conducted using the Python language programming means.

RESULTS

Research sample (participants)

During the primary examination of 108 neurosurgical patients, 5 individuals were excluded due to the presence of exclusion criteria in them. Thus, the sample consisted of 103 patients. POCD was reported in 35 (34%) of them. The age of the test subjects varied from 22 to 77 (mean age — 50) years. The gender distribution was the following: 40 females, 63 males. Eleven patients had diabetes, 44 had arterial hypertension, 35 were smokers. The body mass index of the participants varied from 20 to 41 relative units (median, Me 27.6). The recorded data included the number of years of continuous education at the young age (Me 12.2), the education level (general secondary — 20, incomplete secondary — 1, complete general secondary in 5, secondary vocational in 39, higher in 38) and profession (non-manual workers — 41, manual workers — 62).

The patients were undergoing scheduled surgical intervention in the lumbar segment of the vertebral column, after which, the treatment results were analyzed before and after decompressive laminectomy (in 8) or hemilaminectomy (in 50) with further discectomy, microdiscectomy (in 18) or laminectomy with further transpedicular fixation (in 27).

The duration of anesthetic support was from 120 to 405 minutes (Me 154). The patients were receiving propofol as the preanesthetic medication. As for the muscle relaxants used, they were rocuronium bromide (in 77), suxamethonium bromide (in 10), along with their combination (in 16). The type of anesthesia used was the following: general intravenous with artificial pulmonary ventilation. The combinations of the following medications were used: sevoflurane+fentanyl (in 67); propofol+fentanyl in 14); desflurane+fentanyl (in 12); propofol+fentanyl+sodium oxybutyrate (in 3); sevoflurane+fentanyl+ketamine (in 6).

Primary research outcomes

The results of testing with the MoCA scale before and after surgeries have demonstrated the values ranging from 17 to 30 points (Me — 25 and 23.8 respectively), the Isaac tests — from 17 to 40 points (Me — 32 and 31, respectively), the Munsterberg test — from 7 to 28 points (Me — 16 and 15, respectively).

As for the extra-operative factors, a notable positive correlation was observed between the development of POCD and the age (r=0.53; p <0.01), with moderate one for the body mass index (r=0.35; p <0.01) and for the presence of arterial hypertension (r=0.42; p <0.05). A moderate negative interrelation was found between the number of education years and the development of POCD (r=-0.36; p <0.01). The presence of diabetes does not affect the development of POCD. The coefficient of association for smoking had a low significance level, which does not allow for comprehensive interpreting the obtained results as valid.

Regarding the intraoperative risk factors, the following results were obtained: the type of surgical intervention did not correlate with the development of POCD. The duration of anesthetic support (r=0.02; p <0.01) is also not the factor affecting the development of POCD. A moderate correlation was found for using (as the anesthesia means) the desflurane + fentanyl combination of drugs (r=0.31; p <0.05), mild correlation — for using the sevoflurane+fentanyl + ketamine combination (r=0.25; p <0.05). Using fentanyl together with sevoflurane (r=0.07), propofol (r=-0.1) or sodium oxybutyrate (r=0.05) does not lead to the occurrence of POCD (p <0.05).

Undesirable phenomena

No adverse events were registered.

DISCUSSION

The influence in terms of developing POCD was observed for the age, the body mass index, the presence of arterial hypertension and the number of education years. The most prominent association was found between the age and the development of POCD, which corresponds to already available literature data [4, 5, 8, 9]. Due to the variety of the test group, using this factor, one can extrapolate the obtained data to other patients with vertebral diseases.

The high body mass index and the presence of arterial hypertension also have significantly increased the risks of developing POCD, which correlated with the results of a large number of other research works with the participation of cardiology or trauma patients [10–12]. The presence of moderate interrelation indicates the possibility of influence from the endogenous protective factors, such as the genetic

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markers, the effects of which on the development of POCD still need to be explored.

From the exogenous extra-operative factors, the highest influence was provided by the number of years of education. The detected negative moderate correlation shows that the presence of higher education and long-term learning act as the protective factor, decreasing the probability of developing POCD. Similar data were obtained in other POCD research works [13–15].

As for the diabetes affecting the development of POCD, significantly weaker interrelation was found, which is slightly diverging with the available data on this topic [16, 17]. It is probable that the level of diabetes compensation, the achievement of target glycemia levels and the diseases duration have more significance than the fact of diagnosis itself, due to which, more detailed research is needed for exploring such cause-and-effect associations.

In the latest research works, the data on the effects of smoking on the development of POCD diverge. In one of the research works [18] smoking acts as the protective factor against POCD, while the meta-analysis [9] draws a conclusion on the negative effects of smoking on the cognitive functions in the individuals with past cardiac surgeries. The data obtained in our research, do not allow for completely rejecting or confirming the effects of smoking on the development of POCD.

The association with the duration of anesthetic support was confirmed in multiple research works with cardiology or trauma patients, but in several research works, the data were controversial [16, 19]. The results obtained in our research may indicate that the type of surgery itself (vertebral column surgery) adds its own specific features to the development of POCD. In all appearances, due to the anatomical remoteness of the surgery field and the small blood loss during surgery, the effect of this factor is insignificant, however, further research is required on this issue. Our research has proven that the specific type of vertebral surgery itself does not affect the cognitive functions.

It was found that using fentanyl in combination with desflurane or sevoflurane and ketamine can influence the development of cognitive disorders, for there was a moderate and mild association, respectively. A recent research [20] also contained data obtained that were showing the pathological effect of desflurane and sevoflurane on the cognitive functions.

Comparing the obtained data, a conclusion can be drawn that, when preparing for surgical intervention, it is necessary to collect the past cognitive history of the patient (number of education years, education type, type of work) and comparing it to the forthcoming anesthesiology support. For the elderly patients with multiple concomitant diseases, as well as for patients with low education level, manual type of labor, it is undesirable to use the combinations of desflurane+fentanyl and sevoflurane+fentanyl+ketamine. In patients with several risk factors, the usage of neuroprotective therapy is possible during the pre- and post-operative periods for decreasing the probability of developing POCD.

Based on the data obtained in our research, not all the cases of developing POCD can be explained, especially among young patients without any risk factors. Further research on the endogenous biochemical and genetic risk factors of developing POCD shall allow for drawing a more comprehensive picture of developing this disease and minimizing the risks of cognitive disorders after surgeries.

Research limitations

The clearest limiting factors are the testing conditions: unfavorable environment of the hospital ward, uncomfortable conditions and the presence of other test subjects can significantly affect the results of examining the cognitive functions. In order to minimize this factor, the recommendations include arranging the testing at the same time by a single investigator, in a separate room, after meals and with comfortable temperature and light.

Other limiting factor can be the severity grade of pain syndrome: while having a highly intensive pain, the test subject cannot focus on the test tasks or completely refuses to participate in the testing session. The optimal decision in this case would be the rational use of pain medications.

CONCLUSION

Knowing the risk factors for post-operative cognitive dysfunction will allow for preventing the development of this condition. Based on the obtained results, for older age patients with high body mass index value, with the presence of arterial hypertension and low education level, it is recommended to choose the rational combinations of anesthesia medications and more sparing treatment methods, including the consideration of the possibility of conservative therapy with using neuroprotective drugs.

Further research is required in this field for compiling a more comprehensive picture of the pathogenesis of post-operative cognitive dysfunction.

ADDITIONAL INFORMATION

Author contributions: *V.A. Saltanova*, patient interviewing, statistical data analysis, literature review; *O.A. Kicherova, L.I. Reikhert*, formulation of the research goals and objectives; *Yu.I. Doyan*, development of the study design, formulation of inclusion and exclusion criteria; *N.A. Mazurov*, selection of patients for interview. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Primary Femoro-Popliteal-Tibiofibular Bypass in Patients with Critical Limb Ischemia in the Era of Endovascular Surgery

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ABSTRACT

BACKGROUND: *In the majority of patients with critical ischemia in the lower limbs, the findings include the "multi-level" atherosclerotic lesions in the arteries of the femoral-popliteal-tibiofibular segment. The optimal method of re-vascularisation in this cohort of patients is not defined as of today.* ***AIM:*** *To evaluate the efficiency of conducting the initial autovenous tibiofibular bypass surgery in case of lesions in the arteries of the femoral-popliteal-tibiofibular segment in patients with critical ischemia of the lower limbs.* ***METHODS:*** *The analysis included the results of the initial tibiofibular autovenous bypass surgeries, performed in 112 patients at the Federal State Budgetary Institution "Federal Clinical Center of High Medical Technologies" under the Russian Federal Medical-Biological Agency during the period from 2010 until 2021, of which 25 (22.3%) individuals had the stage III chronic arterial insufficiency in the lower limbs, 87 (77.7%) — stage IV acc. to the Fountain–Pokrovsky classification. The distribution by the atherosclerotic lesion in arteries of the lower limbs with taking into consideration the TASC II classification was the following: type C — in 9 (8.0%), type D — in 103 (92.0%).* ***RESULTS:*** *Within the 30 days period, 4 (3.6%) patients have shown the presence of unfavorable cardio-vascular events, 3 (2.7%) cases resulted in the early high amputation. The perioperative mortality rate was 2.7% (n=3). The primary passability of the tibiofibular autovenous bypass was 91%, 76% and 67% in 1, 3 and 5 years, while the secondary passability was 93%, 80% and 71%; the limb survival rate was 98%, 86% and 81,5%; the overall survival of the patients was 88.5%, 81% and 70%, respectively.* ***CONCLUSION:*** *The initial tibiofibular autovenous bypass surgeries (bypass first) represent the effective and safe method of surgical treatment for atherosclerotic lesions in the arteries of the femoral-popliteal-tibiofibular segment in patients with critical ischemia of the lower limbs. Open-access surgeries in the era of endovascular surgery can be used as the first line therapy with comparable direct and remote results.*

Keywords: *critical ischemia of the lower limbs; femoral-popliteal-tibiofibular arterial segment; tibiofibular autovenous bypassing.*

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BACKGROUND

The diseases of peripheral arteries are widespread worldwide and affect 113 mln people aged from 40 years and older, of which 42.6% live in the countries with low and medium social-demographic index [1]. The occurrence rate for the diseases of peripheral arteries has increased by 72% during the period from 1990 until 2019, taking into consideration the 45% overall population growth [2, 3]. The five-year cumulative rate of clinical worsening from the asymptomatic disease of peripheral arteries to the intermittent claudication is 7%, while from the intermittent claudication to critical ischemia in the lower limbs — 21% [4]. As of today, in the whole world, every year approximately 25 000 high amputations of the limbs are carried out for the reason of critical ischemia in the lower limbs, which significantly decreases the life duration in this cohort of patients [5]: the overall mortality level is reaching 15% in 1 year, 24% in 2 years and 43% in 5 years [6]. According to the data from multiple authors, critical ischemia of the lower limbs is associated with the development of cardio-vascular events, including the period of 30 days after re-vascularisation [7–9]. It is undeniable that the

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Первичное шунтирование при поражении артерий бедренно-подколенно-берцового сегмента у пациентов с критической ишемией нижних конечностей в эру эндоваскулярной хирургии

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АННОТАЦИЯ

Обоснование. *У большинства пациентов с критической ишемией нижних конечностей выявляется «многоэтажное» атеросклеротическое поражение артерий бедренно-подколенно-берцового сегмента. Оптимальный метод реваскуляризации у данной когорты пациентов на сегодняшний день не определён.* ***Цель*** *— оценить эффективность выполнения первичного аутовенозного берцового шунтирования при поражении артерий бедренно-подколенно-берцового сегмента у пациентов с критической ишемией нижних конечностей.* ***Методы.*** *Проанализированы результаты первичных берцовых аутовенозных шунтирований, выполненных 112 пациентам в ФГБУ ФКЦ ВМТ ФМБА России в период с 2010 по 2021 год, из них 25 (22,3%) человек имели III стадию хронической артериальной недостаточности нижних конечностей, 87 (77,7%) — IV стадию по классификации Фонтейна–Покровского. Распределение по атеросклеротическому поражению артерий нижних конечностей с учётом классификации TASC II было следующим: тип C — у 9 (8,0%), тип D — у 103 (92,0%).* ***Результаты.*** *В течение 30-дневного срока у 4 (3,6%) пациентов были выявлены неблагоприятные сердечно-сосудистые события, в 3 (2,7%) случаях выполнена ранняя высокая ампутация. Периоперационная смертность — 2,7% (n=3). Через 1, 3 и 5 лет первичная проходимость берцовых аутовенозных шунтирований составила 91%, 76% и 67%, в то время как вторичная проходимость — 93%, 80% и 71%; показатель сохранения конечности — 98%, 86% и 81,5%; общая выживаемость пациентов — 88,5%, 81% и 70% соответственно.* ***Заключение.*** *Первичные берцовые аутовенозные шунтирования являются эффективным и безопасным методом хирургического лечения атеросклеротического поражения артерий бедренно-подколенно-берцового сегмента у пациентов с критической ишемией нижних конечностей. Открытые хирургические операции в эру эндоваскулярной хирургии могут быть использованы в качестве первой линии терапии с сопоставимыми непосредственными и отдалёнными результатами.*

Ключевые слова: *критическая ишемия нижних конечностей; бедренно-подколенно-берцовый артериальный сегмент; берцовое аутовенозное шунтирование.*

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main method for treating the patients with critical ischemia in the lower limbs is the re-vascularisation of the lower limbs [10]. In the majority of such patients, a “multi-level” atherosclerotic lesion is found in the arteries of the femoral-popliteal-tibiofibular segment [11], which is why the issue of selecting the reconstructive interventions as of today remains topical and discussible.

Research aim — to analyze the 12-years experience of performing the initial tibiofibular autovenous bypass surgeries in patients with critical ischemia in the lower limbs at the premises of the Federal State Budgetary Institution “Federal Clinical Center of High Medical Technologies” under the Russian Federal Medical-Biological Agency (FSBI FCC HMT under the Russian FMBA) and to evaluate their efficiency.

METHODS

Research design

Single-center non-randomized retrospective observational research.

Conformity criteria

Inclusion criteria: the presence of critical ischemia in the lower limbs (resting pain or trophic defects in the shin and in the foot); "multi-level" atherosclerotic lesion in the femoral-popliteal-tibiofibular arterial segment; absence of previously conducted surgeries in the ipsilateral limb; the presence of the greater saphenous vein applicable for bypassing.

Non-inclusion criteria: intermittent claudication of the lower limbs; isolated lesions in the shin arteries; absence of at least one passable tibial artery for shaping the distal anastomosis; the presence of a vast trophic defect in the zone of formation of the planned anastomosis.

Research facilities

The examination was carried out at the Vascular Surgery Department of the Center for Cardio-Vascular and Endovascular Surgery of the FSBI FCC HMT under the Russian FMBA.

Research Duration

The research work was carried out for 12 years (during the period from January 2010 until December 2021).

Medical procedure description

During the pre-operative period, all the patients underwent the procedures of measuring the ankle-brachial index, the stratification by the scale of the severity of morphological damage in the tissues of the foot, the perfusion of the lower limbs, the severity of the infectious process (Wound, Ischemia, foot Infection, Wifi, 2014) with further staging the clinical risk of high amputation, as well as the ultrasound examination of the arteries and veins (for the evaluation of the possibilities of using the greater saphenous vein as the conduit) and the contrasted visualization of arteries (angiography / multispiral computed tomography of vessels, MSCT-AG) of the lower limbs. Further procedures included the modification of risk factors, prescribing or correcting the antihypertensive therapy, the insulin therapy, the intake of statins, of antiaggregants and the anticoagulants.

All the surgical interventions were carried out under the endotracheal anesthesia. In 100% of the cases, the proximal anastomosis with autovenous bypass was formed from the common femoral artery, while for the bypassing artery, any other passable artery with better outflow was used. The vast majority of surgeries was carried out using the *in situ* method, but also the compound and reversed autoveins were used as the conduit (the characteristics of all the tibiofibular autovenous bypass surgeries are provided in table 1).

Statistical analysis

The statistical analysis and data processing were carried out using the Statistica v.10.0 software by StatSoft Inc. (USA) using the parametric (t-Student's test) and the nonparametric (Kaplan–Meier survival analysis) methods. The statistical significance was set as $p < 0.05$.

RESULTS

Research sample (participants)

A total of 112 initial tibiofibular autovenous bypass surgeries were performed in 94 (83.9%) male patients and 18 (16.1%) female patients. The mean age of the patients was 66.3±9.1 years (ranging from 44 to 90 years). Stage III chronic arterial insufficiency of the lower limbs acc. to the classification by Fountain–Pokrovsky was diagnosed in 25 (22.3%) patients, stage IV — in 87 (77.7%). The mean value of the ankle-brachial index before surgical intervention was 0.15±0.08.

The stratification of the patients using the Wifi scale (2014) with staging the clinical risk of high amputation is provided in table 2. The distribution of patients by the atherosclerotic lesion in the arteries of the

Table 1

Types of tibiofibular bypass surgeries

Type of bypassing	Autovenous conduit, *n* (%)		
	in situ	reversed	compound
Femoral-anterior tibial	22 (19.6)	2 (1.8)	0 (0.0)
Femoral-fibular	34 (30.3)	7 (6.3)	2 (1.8)
Femoral-posterior tibial	34 (30.3)	3 (2.7)	3 (2.7)
Femoral-tibioperoneal	5 (4.5)	0 (0.0)	0 (0.0)

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Table 2

Stratification of patients using the Wifi scale with determining the clinical risk stage for high amputation

Clinical stage	Wifi scale range of values	*n* (%)	
II (low risk)	0-2-0	5 (4.4)	25 (22.3)
	0-3-0	20 (17.9)	
III (medium risk)	1-2-0	6 (5.4)	70 (62.5)
	1-2-1	8 (7.1)	
	1-3-0	19 (17.0)	
	1-3-1	28 (25.0)	
	2-2-0	9 (8.0)	
IV (high risk)	2-2-2	2 (1.7)	17 (15.2)
	2-3-1	3 (2.7)	
	2-3-2	3 (2.7)	
	3-3-0	3 (2.7)	
	3-3-1	3 (2.7)	
	3-3-2	3 (2.7)	

lower limbs acc. to the TASC II classification was the following: type C was diagnosed in 9 (8.0%) individuals, type D — in 103 (92.0%). All the patients enrolled into the research had a number of concomitant diseases and past surgical interventions (table 3).

The main research outcome

Within the framework of this scientific research, we have tracked and analyzed the direct (30-days) and the remote (5-years) results of tibiofibular autovenous bypass surgeries.

In 7 (5.9%) cases of initially selected 119 patients for bypass surgeries, the decision was to carry out the hybrid intervention due to the technical failure (conversion). These patients were excluded from the further analysis. The mean value of the ankle-brachial index after the surgical intervention was 0.94±0.16. Within the period of 30 days, 4 (3.6%) operated patients were diagnosed with unfavorable cardio-vascular events (three acute myocardial infarctions and a single acute cerebrovascular accident) and in 3 (2.7%) cases, the early high amputation was done. The perioperative mortality was 2.7% (3 patient), the reasons of which became the abovementioned acute myocardial infarctions (2; 1.8%) and an acute cerebrovascular accident (1; 0.9%). Local complications in the area of the postoperative wounds were detected in 11 (9.8%) patients.

The remote results included the primary and the secondary passability, the limb survival and the overall survival. The primary passability of the tibiofibular autovenous bypasses was 91%, 76% and 67% in 1, 3 and 5 years (p <0.05), while the secondary passability of the bypasses — 93%, 80% and 71%,

Table 3

Comorbid disorders in patients with critical ischemia of the lower limbs

Disorders	*n* (%)
Arterial hypertension	105 (93.8)
Ischemic heart disease	60 (53.6)
Re-vascularisation of the myocardium	18 (16.1)
Atrial fibrillation	13 (11.6)
Past acute cerebrovascular accident	18 (16.1)
Carotid re-vascularisation	14 (12.5)
Diabetes	31 (27.7)
Chronic kidney disease stage III–V	18 (16.1)
Chronic obstructive pulmonary disease	10 (8.9)
Re-vascularisation of the contralateral limb	26 (23.2)

respectively (p <0.05) (Fig. 1, 2). The value of the limb survival parameter among the patients was 98%, 86% and 81.5% in 1, 3 and 5 years (p <0.05) (Fig. 3), the overall survival of the patients — 88.5%, 81% and 70%, respectively (p <0.05) (Fig. 4).

DISCUSSION

During the last 10 years, various international and Russian scientific communities have issued more than 20 consensus documents, related to the problems of treating critical ischemia in patients with atherosclerotic lesions in the arteries of the lower limbs. The successfully conducted arterial reconstructive surgery not only saves the limb and improves the quality of life, but also saves the life of the patient.

The optimal tactics of surgical treatment for the patients with critical ischemia in the lower limbs in cases of multi-level extensive lesions in the arteries of the lower limbs still remains a topic of multiple research works, including the international randomized multi-center ones (BEST-CLI, BASIL-2) [12, 13]. In recent years, the rates of conducting the endovascular interventions as the strategy of first-line re-vascularisation has significantly increased [14, 15]. Despite this tendency, the results of our research present the convincing data in favor of using the tactics of "bypass first" for the lesions of the arteries in the femoral-popliteal-tibiofibular segment in patients with critical ischemia of the lower limbs. The evaluation of the significance of the strategy for re-vascularisation of the lower limbs in such patients is carried out, generally, by the direct (perioperative) and remote results of reconstructive interventions. In case of the presence of a number of technical possibilities (greater saphenous vein applicable for bypass, passable tibial artery for the formation of the distal anastomosis, absence of vast

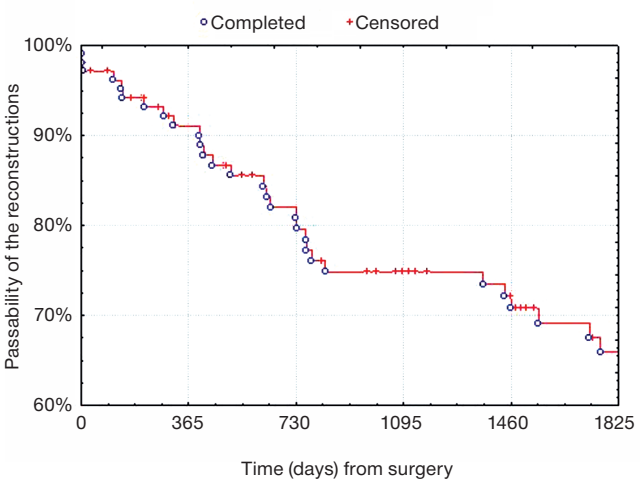

Fig. 1. Remote results: primary passability.

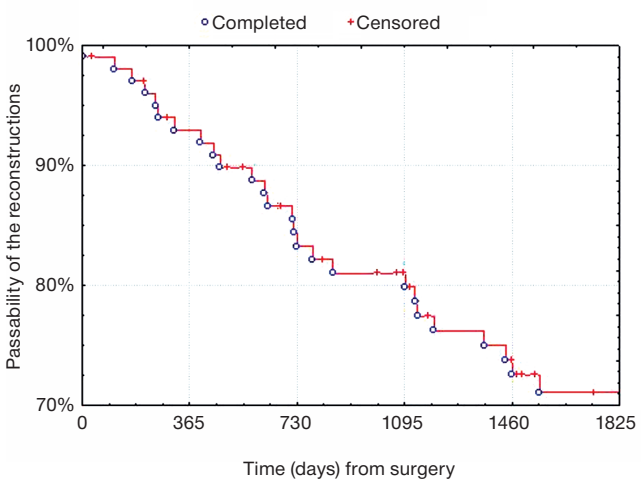

Fig. 2. Remote results: secondary passability.

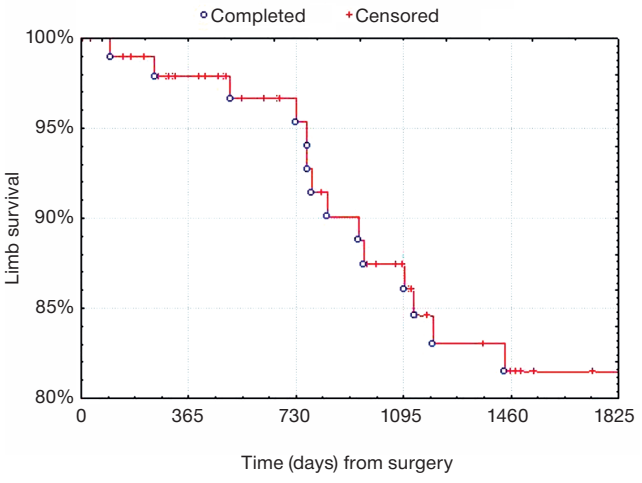

Fig. 3. Remote results: limb survival.

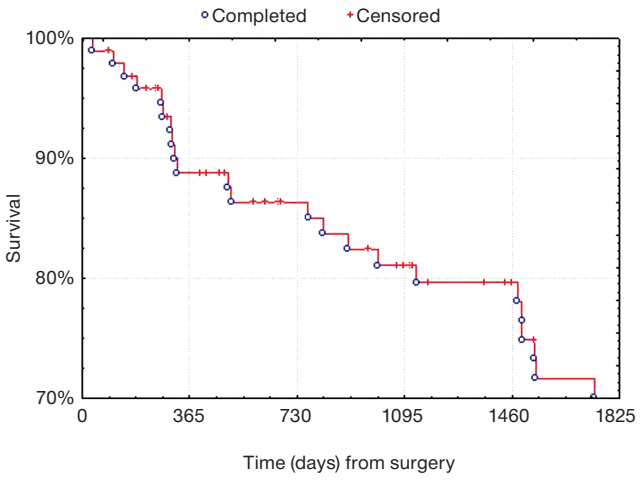

Fig. 4. Remote results: survival.

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trophic defects in the zone of the planned anastomosis formation in the shin) practically in all the patients after the femoral-tibiofibular autovenous bypass surgery we managed to achieve the positive result in the early follow-up period.

The perioperative complications in our research have demonstrated the minimal values for 30-days mortality (2.7%), for high amputation (2.7%) and for the unfavorable cardio-vascular events (3.6%). These data are comparable to the ones from the global research works and indicate the high safety of the femoral-tibiofibular bypass surgeries in patients with critical ischemia of the lower limbs. Thus, in the BEST-CLI research [12], in the cohort of patients with the greater saphenous vein applicable for bypass, between the groups of the open-access and the endovascular treatment, no significant differences were demonstrated in 30 days regarding the rates of the main unfavorable cardio-vascular events (4.6% and 3.2%, respectively) and the perioperative mortality (1.7% and 1.3%, respectively). In the well-known Finnvasc register, the 30-days mortality was 3.1%, while the 30-days high amputation rate was 6.3% [16].

High levels of the rate of limb survival and of the overall survival, which were analyzed in our research in the remote period, also correspond to the worldwide research data published in the last several years. Thus, in the BASIL-2 research, the limb survival rate in the group of autovenous bypass surgeries was 80% in 5 years, however, it is worth keeping in mind that more than half of the patients have deceased within this period after the randomization [13]. Among 38 470 patients with critical ischemia of the lower limbs, which underwent the infrainguinal bypassing or endovascular interventions, the evaluation of the 30-days survival rate was 98%, while the 2- and 5-years survival rate — 81% and 69%, respectively [17].

CONCLUSION

The initial tibiofibular autovenous bypass operation (the bypass first surgery) is an effective and safe method of surgical treatment for atherosclerotic lesions in the arteries of the femoral-popliteal-tibiofibular segment in patients with critical ischemia of the lower limbs. In the era of endovascular surgery, open-access surgeries can be used as the first line operations with the comparable direct and remote results.

ADDITIONAL INFORMATION

Author contributions: *A.Yu. Burov*, *E.R. Lysenko*, *O.G. Gryaznov*, performing surgical operations on patients; *A.Yu. Burov*, general concept, processing and discussion of the study results, writing the text of the article; *E.V. Gulyaeva*, *R.B. Abasov*, search and analytical work, writing the text of the article; *K.A. Knyazeva*, *E.D. Malyutina*, performing ultrasound diagnostics on patients in the postoperative period, processing and discussion of the study results; *E.R. Islyamov*, search and analytical work, processing and discussion of the study results; *E.R. Lysenko*, general concept, management of patient treatment and discussion of the study results, editing the text. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The Tactics of Weaning from Cardiopulmonary Bypass with Blood-saving Technique in Cardiac Surgery

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ABSTRACT

BACKGROUND: *Cardiac surgery under cardiopulmonary bypass is typically characterized by significant blood loss and the need for donor red blood cell transfusions. In addition to the inflammatory response, hemodilution, hypocoagulation, and blood loss significantly contributes to the development of perioperative anemia associated with the weaning from the cardiopulmonary bypass.* ***AIM:*** *Optimization of weaning from cardiopulmonary bypass to reduce blood loss during cardiac surgery.* ***METHODS:*** *Patients undergoing cardiac surgery under cardiopulmonary bypass (n=62) were divided into two groups. In the study group (n=31), all blood from cardiopulmonary bypass circuit was returned to the patient's central vein at the end of the cardiopulmonary bypass. In the comparison group (n=31), a standard method of pushing a residual blood volume from the cardiopulmonary bypass circuit with normal saline was used. Laboratory and instrumental data were analyzed.* ***RESULTS:*** *Intraoperative blood loss in the study group was significantly lower than in the comparison group (500 [470–520] ml versus 800 [760–830] ml, p=0.0001). Twenty-four hours after surgery, creatinine, alanine aminotransferase, and amylase concentrations were higher in the study group than in the comparison group. At the end of surgery, the study group also had higher cardiac index (3.1 [2.8–3.6] versus 2.8 [2.6–3.1] l/m^2 per minute, p=0.018) and global ejection fraction (28 [22–31] versus 22 [19–24]%), p=0.011). No adverse events or reactions were registered during the study.* ***CONCLUSION:*** *Complete blood return after cardiopulmonary bypass results in higher hemoglobin and hematocrit levels in the early postoperative period, accompanied by less blood loss and higher cardiac index and global ejection fraction after the main stage of the surgery without significant adverse events.*

Keywords: *artificial circulation; blood loss; hemohydrobalance; cardiosurgery.*

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BACKGROUND

The procedure of cardiopulmonary bypass (CPB) is a potent stress for the organism, which may be accompanied by pronounced pathophysiological reactions [1]. CPB may result in the development of systemic inflammatory response, anemia, increased risks of perioperative hemorrhages due to the hemodilution (a decrease in the number of red blood cells in blood plasma resulting from the increase in the total plasma volume), due to the decreased levels of coagulation factors and due to the dysfunction of platelets [2].

Cardiac surgery is considered the leading field by the number of post-operative blood loss and by the development of post-operative hemorrhages. An important step of the CPB is its termination, for the volume of blood remaining after the CPB procedure in the oxygenator and the pipelines, significantly affects the development of the post-operative anemia. However, currently the medical published literature contains no

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Тактика завершения процедуры искусственного кровообращения в рамках кровосберегающей концепции при кардиохирургических операциях

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АННОТАЦИЯ

Обоснование. *Кардиохирургические вмешательства в условиях искусственного кровообращения обычно характеризуются значительной кровопотерей и потребностью в переливании донорских компонентов крови. Помимо системной воспалительной реакции, гемодилюции и гипокоагуляции, важный вклад в развитие периоперационной анемии вносит кровопотеря, связанная с этапом завершения искусственного кровообращения.* ***Цель*** *— оптимизация этапа завершения искусственного кровообращения для уменьшения кровопотери при кардиохирургических операциях.* ***Методы.*** *Прооперированные в условиях искусственного кровообращения пациенты (n=62) разделены на две группы. В основной группе (n=31) по окончании процедуры искусственного кровообращения весь объём крови из всех магистралей аппарата искусственного кровообращения возвращали в центральную вену пациента. В группе сравнения (n=31) использовали стандартный метод отдачи остаточной крови из контура искусственного кровообращения с помощью вытеснения физиологическим раствором. Анализировали данные лабораторных и инструментальных методов исследования.* ***Результаты.*** *Интраоперационная кровопотеря в основной группе была значимо ниже, чем в группе сравнения (500 мл [470–520] против 800 мл [760–830], p=0,0001). Через 24 часа после операции концентрация креатинина, аланинаминотрансферазы и амилазы были выше в основной группе, чем в группе сравнения. В конце операции в основной группе также были выше сердечный индекс (3,1 [2,8–3,6] против 2,8 [2,6–3,1] мл/мин/м^2, p=0,018) и глобальная фракция изгнания (28 [22–31] против 22 [19–24]%, p=0,011). Нежелательные явления и реакции во время проведения исследования отсутствовали.*

Заключение. *Полный возврат крови после искусственного кровообращения в организм пациента приводит к увеличению показателей гемоглобина и гематокрита в раннем послеоперационном периоде, сопровождается меньшим объёмом кровопотери и более высокими уровнями сердечного индекса и глобальной фракции изгнания после основного этапа операции на фоне отсутствия значимых нежелательных явлений.*

Ключевые слова: *искусственное кровообращение; кровопотеря; гемогидробаланс; кардиохирургия.*

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algorithms for finishing this procedure. The blood-saving techniques in cardiac surgery include the transfusing blood from CPB circuit to the Cell Saver [3]. This method is considered expensive and unavailable in some centers, necessitating optimization of the weaning from the CPB for decreasing the blood loss after heart surgery.

In cases of significant blood loss, for correcting the anemia, generally, the donor blood components are being used, though recently more attention in the medical literature is gained by various aspects of the necessity to minimize the transfusions of donor blood components [4]. This is related to the results of a large number of research works confirming that the transfusion of donor blood components is accompanied by an increase in the number of post-operative complications and in the number of hospitalization days, by the increase in the morbidity and mortality rates, as well as the increase in the costs of treating the patient [5].

Research aim — Optimization of weaning from cardiopulmonary bypass to reduce blood loss during cardiac surgery.

METHODS

Research design

This research is open-label, prospective and randomized.

Conformity criteria

Inclusion criteria: patients admitted to the Cardiosurgery Department of the Federal State Budgetary Institution "Federal Clinical Center of High Medical Technologies" under the Federal Medical-Biological Agency (FSBI FCC HMT under the Russian FMBA), of any gender, aged older than 18 years, in which the scheduled cardiosurgery intervention is planned in the settings of artificial circulation.

Exclusion criteria: emergency surgical intervention.

Non-inclusion criteria: aged under 18 years; individuals refusing to participate in the research.

Research facilities

The research was carried out within the premises of the Center for Cardio-Vascular and Endovascular Surgery of the FSBI FCC HMT of the Russian FMBA.

Research Duration

The research was carried out during the period from October 2023 until March 2024.

Medical procedure description

The research has enrolled 62 adult cardiosurgery patients operated in the settings of CPB, which were divided into two groups. In the main group (n=31) upon the end of CPB, the whole volume of blood from all the pipelines of the artificial circulation equipment was returned into the central vein of the patient via the laboratory shunt pipe attached to the aortic cannula. In the comparison group (n=31), a traditional method was used that included the substitution of residual blood in the pipelines of the bypass after the completion of CPB. With the traditional method, after the end of the CPB procedure, the volume of blood remaining in the cardiotomy reservoir was returned to the vascular system of the patient via the aortic cannula. The blood remaining in the pipelines was relocated by displacing with an additional volume of normal saline (approximately 400 ml). After the decannulation of the aorta, the volume of blood remaining in the pipelines, was discarded.

The methods of perfusion and anesthetic management did not differ between the groups: for the induction of anesthesia, Midazolam was used (0.1±0.02 mg/kg) along with Propofol (1.1±0.08 mg/kg), Fentanyl (7.0±0.3 μg/kg), Rocuronium bromide (0.9±0.03 mg/kg); for maintaining the anesthesia — Sevoflurane (0.5–1 MAC, where the MAC is the minimal alveolar concentration); Fentanyl (1,9±0.3 μg/kg per hour), Propofol (with the target concentration being 1.5±0.1 mg/ml during the CPB) and Rocuronium bromide (0.3±0.03 mg/kg per hour).

Perfusion methods: volumetric flow rate of the perfusion — 2.5 l/m^2 per minute, non-pulsatile mode, temperature mode: 35.8–36.7°C.

The patients were receiving blood cardioplegia using the Calafiore's method (cardioplegia type 1) or crystalloid cold antegrade cardioplegia by Custodiol solution with the separate cannulation of the upper and the lower vena cava and with further removal of the cardioplegia solution into the external drainage via the coronary sinus (cardioplegia type 2).

The prime volume of CPB was: Gelofusin (500 ml), Sterofundin (750 ml), 15% Mannitol solution (150 ml) and 5% Sodium hydrocarbonate solution, $NaHCO_3$ (100 ml).

Methods for registration of outcomes

The parameters of the central blood circulation were measured using the PiCCO technology (Pulse index Continuous Cardiac Output) and the following parameters were analyzed: the cardiac index, the global ejection fraction, the index of the global function of the left ventricle, the extravascular lung water and the systemic vascular resistance index.

None of the patients in the research had received the transfusion of the donor blood components.

An analysis of the intraoperative data included the acid-base balance, the central (transpulmonary thermodilution method, PiCCO technology) and

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the systemic hemodynamics before the operation, at the 5, 30 and 60 minutes stages of CPB and after finishing the CPB along with the sternal closure.

During the post-operative period, the analyzed values included the parameters of the general (clinical) and the blood biochemistry panels, the acid-base balance, the duration of mechanical ventilation, the length of stay in the Intensive Care Unit and the mortality rates.

Statistical analysis

The statistical analysis of the data was done using the SPSS 26.0 software pack (IBM Corp., New York, USA). The continuous and the categorical variables were presented as the median (Me) and the quartiles (25%; 75%) or *n* (%) depending on the type of data. The comparison of the quantitative characteristics among the groups was carried out using the Mann-Whitney test. For evaluating the significance of the differences between the categorical variables, the $\chi 2$ (2×2) tests were used with the Yates's correction. When evaluating the dynamic intragroup data, the Wilcoxon criterion was applied. When checking the statistical hypotheses, the statistical significance was established with the *p* value of <0.05.

RESULTS

Research sample (participants)

The patients from the Center for Cardio-Vascular and Endovascular Surgery of the FSBI FCC HMT of the Russian FMBA, operated in the settings of artificial circulation (*n*=62), were divided into two groups — the main one (*n*=31; after finishing the CPB, the whole blood volume from all the pipelines of the artificial circulation equipment returning to the central vein of the patient via the laboratory shunt pipeline attached to the aortic cannula) and the comparison group (*n*=31; traditional method of displacing the residual blood from the artificial circulation equipment pipelines after the completion of CPB).

The groups were comparable by the age, the gender, the duration of CPB, the duration of surgery, as well as by the baseline values of the biochemistry and clinical hematology panels, as well as by the coagulation panel findings, by the data from the instrumental examinations, by the spectrum of conducted surgical interventions, by the time of myocardial ischemia and by the concomitant diseases (table 1, 2).

Primary findings

No significant differences were found in the intraoperative hemoglobin and hematocrit levels between the groups (table 3).

In the main group, during the surgery, an increase was found in the volume of fluid administered during the CPB (table 4). It was probably related to the necessity of supporting the sufficient filling volume for the cardiotomy reservoir at the main phase of surgery.

The total intraoperative blood loss in the main group was significantly lower comparing to the one in

Table 1

Demographical and laboratory data

Parameter	Group		*p*
	Main *n*=31	Comparison *n*=31	
Age, years	67 [57–69]	65 [56–69]	0.405
Body weight, kg	84 [75.8–95.0]	80 [71–90]	0.337
Body mass index, kg/m^2	28.9 [26.5–36.6]	26.7 [24.9–30.8]	0.062
Males, *n* (%)	19 (61)	23 (74)	0.277
Creatinine, μmol/l	89 [80–106]	91 [75–99]	0.756
Alanine aminotransferase, u/l	17 [16–27]	19 [13–24]	0.820
Amylase, u/l	53 [42–90]	84 [35–104]	0.846
Red blood cells, thous./μl	4.81 [4.35–4.95]	4.76 [4.37–5.01]	0.947
Hemoglobin, g/l	139 [131–147]	143 [129–151]	0.564
Hematocrit, %	41.8 [38.4–44.0]	41.5 [37.5–45.6]	0.830
Platelets, thous./μl	227 [195–271]	242 [187–286]	0.679
Prothrombin, %	104 [93–108]	99 [91–104]	0.188
Fibrinogen, g/l	5.7 [4.3–7.5]	5 [4.2–6.7]	0.228

Table 2

Characterization of surgeries

Parameter	Group		*p*
	Main *n*=31	Comparison *n*=31	
Plegia type 1, *n* (%)	23 (74)	22 (71)	0.766
Coronary artery bypass grafting, *n* (%)	2 (6.5)	2 (6.4)	0.380
Valve, *n* (%)	22 (71)	26 (83.9)	
Combined, *n* (%)	7 (22.5)	3 (9.7)	
CPB duration, min	58 [46–81]	63 [53–81]	0.436
Duration of myocardial ischemia, min	43 [33–58]	50 [40–60]	0.406

Note. CPB — cardiopulmonary bypass.

Table 3

Comparison of intraoperative parameters

Parameter	Group		*p* Mann–Whitney test
	Main *n*=31	Comparison *n*=31	
Beginning of surgery			
Hemoglobin, g/l	128 [116–130]	124 [113–131]	0.917
Hematocrit, %	38 [35–39]	36 [33–37.5]	0.086
5 minutes of CPB			
Hemoglobin, g/l	92 [82–100]	90 [80–103]	0.860
Hematocrit, %	26.5 [22.5–30.5]	24 [20–26.5]	0.138
30 minutes of CPB			
Hemoglobin, g/l	96 [87–102]	91 [80–104]	0.397
Hematocrit, %	28 [23–29]	23 [21–26]	0.062
60 minutes of CPB			
Hemoglobin, g/l	96 [83–103]	93.5 [86–105]	1.000
Hematocrit, %	29 [21–32.5]	26 [23.3–26.8]	0.256
After CPB			
Hemoglobin, g/l	105 [98–113]	105 [94–116]	0.920
Hematocrit, %	31 [27–34]	27 [25–32]	0.108

Note. CPB — cardiopulmonary bypass.

the comparison group. This is related to the fact that when using the "standard" method for finishing the AC procedure, approximately 300 ml of blood mixed with physiological solutions remains in the oxygenator and in the pipelines.

In the main group, significant difference was found between the levels of hemoglobin and hematocrit during the first post-operative 24h.

The levels of creatinine, alanine-aminotransferase and amylase in 24 hours after surgery were significantly higher in the main group than in the comparison group, with this, all the parameters were within the reference ranges. We have also found a tendency to later extubation in the main group. The hydrobalance values during the first post-operative 24h did not significantly differ between the groups. Additional evaluation was conducted for the volume of primary filling (ml/kg of the body weight of the patient) and for the intraoperative balance: no significant difference was found between these parameters (see table 4).

The cardiac output parameters before the sternal closure between the groups did not significantly differ. After the sternal closure, the cardiac index and the global ejection fraction were significantly higher in the main group with the comparable dosages of catecholamines (table 5). In the comparison group, the index of the global function of the left ventricle has significantly decreased comparing to the baseline value.

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Table 4

The comparison of the parameters during the first post-operative 24h

Parameter	Group		*p* Mann–Whitney test
	Main *n*=31	Comparison *n*=31	
Creatinine, μmol/l	106 [78–125]	85 [73–105]	0.015*
Alanine aminotransferase, u/l	24 [16–52]	18 [12–27.3]	0.045*
Amylase, u/l	98 [68–276]	60 [44–140]	0.009*
Red blood cells, thous./μl	3.9 [3.5–4.2]	3.65 [3.22–4.06]	0.309
Hemoglobin, g/l	116 [104–124]	103.5 [93–119]	0.028*
Hematocrit, %	33 [30–36]	29.5 [25.5–33]	0.014*
Platelets, thous./μl	158 [119–207]	170 [148–219]	0.319
MV less than 6 h, *n* (%)	11 (35.5)	5 (16)	0.069
Blood loss, ml	500 [470–520]	800 [760–830]	0.001*
Hemohydrobalance, ml • intraoperative • per 24 h	 1240 [600–1893] 1475 [1013–1725]	 1150 [800–1513] 1075 [450–1725]	 0.081 0.135
Drainage tubes, ml	250 [190–335]	250 [187–320]	0.704
Volume of administered fluid during the CPB, ml	2000 [1800–2300]	1833 [1700–1800]	0.003*
Prime, ml/ kg	22.5 [20.68–26.13]	22.78 [20.9–27.05]	0.539
Intraoperative fluid balance, ml/kg	13.34 [9.72–18.12]	16.66 [12.62–20.62]	0.203

Note. MV — mechanical ventilation; CPB — cardiopulmonary bypass. * parameters achieving the statistical significance.

Table 5

Parameters of the central blood circulation

Parameter	Group		*p* Mann–Whitney test
	Main *n*=31	Comparison *n*=31	
Before sternal closure			
Dopamine, μg/kg per minute	4.64 [4–5]	4.58 [4–5]	0.752
CI, l/m^2 per minute	3.1 [2.8–3.3]	3.35 [3.0–3.6]	0.440
GEF, %	26 [21–30]	23 [18–28]	0.185
IGF, ml/m^2	761 [660–824]	753 [665–900]	0.683
EVLW, ml/kg	8 [7.5–9.5]	8 [7–10]	0.618
SVRI, dynes*sec*cm^{-5}/m^2	1709 [1400–2000]	1365 [1300–1592]	0.157
After sternal closure			
CI, l/m^2 per minute	3.1 [2.8–3.6]	2.8 [2.6–3.1]	0.018*
GEF, %	28 [22–31]	22 [19–24]	0.011*
GEF, >25%, *n* %	17 (55)	5 (16)	0.001*
IGF, ml/m^2	775 [643–872]	647 [615–820]	0.142
EVLW, ml/kg	9 [8.5–11.0]	9 [7–10]	0.097
SVRI, dynes*sec*cm^{-5}/m^2	1800 [1400–2153]	1974 [1624–2385]	0.386

Note. CI — cardiac index; GEF — global ejection fraction; IGF — index of the global function of the left ventricle; EVLW — extravascular lung water; SVRI — systemic vascular resistance index. * parameters achieving the statistical significance.

Undesirable phenomena

There were no significant adverse events during the complete blood return after CPB into the organism of the patient during the ten days period.

DISCUSSION

Complete blood return after cardiopulmonary bypass results in higher hemoglobin and hematocrit levels in the early postoperative period, accompanied by less blood loss and higher cardiac index and global ejection fraction after the main stage of the surgery. The increase in the hemohydrobalance at the intraoperative period in the patients operated in the settings of CPB, can contribute to the development of multiorgan dysfunction.

The results obtained during this research confirm the high priority of the blood saving tactics, for significantly higher values were demonstrated for hemoglobin and hematocrit during the first post-operative 24h in the group of patients, in which a complete blood return was done from the pipelines of the artificial circulation equipment into the organism. This matches to the numerous literature data on the practicability and the necessity of implementing the blood-saving technologies into the routine surgery practice [6]. Based on the research results, a significant decrease of the intraoperative blood loss was achieved, which contributed to the decrease in the probability of using the donor blood components. Besides, in the main group, higher values were shown for the cardiac index in the post-perfusion period. The integrity of the contractile function is one of top-priority tasks among the cardiosurgery patients, while its decrease is directly related to the increase in the number of complications during the post-operative period along with the increased in-hospital mortality [7].

According to the data from our research work, in the main group, the fluid balance was significantly higher than in the comparison group one, which, on the one hand, combined with the higher values of red blood, was resulting in the improvement of the cardiac index, while on the other — it has entailed all the drawbacks of increased cumulative hydrobalance. Indeed, achieving the balance between the limitation in the volume of infusion and maintaining the adequate preload periodically can pose a certain problem.

It is known that the liberal infusion tactics, especially with a background of systemic inflammatory response syndrome in cardiac surgery, may result in the development of interstitial edema and multi-organ dysfunction [8]. The higher fluid balance group had higher levels of creatinine, amylase, and alanine aminotransferase during the first 24 hours after surgery, as well as a tendency toward longer (more than 6 hours) postoperative mechanical ventilation. These data completely match to the results from a number of research works, where it was proven that higher fluid balance increases the ventilation time, while the prolong mechanical ventilation increases the risk of unfavorable outcome [9].

One of the variants for optimizing the CPB finishing stage with following the tactics of maximal blood saving without increasing the cumulative hydrobalance is the usage of the autotransfusion equipment and washing off the red blood cells remaining in the CPB circuit with removing the excess fluid [10], however, this method leads to the additional trauma for the blood corpuscles and, according to the data from some authors, can worsen the treatment results [11]. Indeed, the optimal approach to managing the cardiosurgery patients, operated in the settings of CPB, is the maximal blood-saving tactics [12] combined with a decreased volume of perioperative infusion therapy. The present trial has demonstrated the method for the possible increase in the values of the cardiac index and for decreasing the blood loss during the post-operative period, which, in turn, can reduce the risk of developing complications among the cardiosurgery patients.

Thus, the complete return of blood after the CPB via the laboratory shunt loop into the organism of the patient results in an increase in the values of hemoglobin and hematocrit within the early post-operative period, being accompanied by lesser volume of blood loss and higher levels of the cardiac index and of the global ejection fraction after the main surgery phase. Positive hydrobalance could lead to the development of multi-organ dysfunction.

Research limitations

The research work has a number of the following limitations: single center involved with a small sample of patients; the patients were admitted for scheduled surgical intervention and had no severe concomitant diseases.

CONCLUSION

Thus, the complete blood return after cardiopulmonary bypass results in higher hemoglobin and hematocrit levels in the early postoperative period, accompanied

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by less blood loss and higher cardiac index and global ejection fraction after the main stage of the surgery. Also not being associated with significant adverse events.

ADDITIONAL INFORMATION

Author contributions: *Ya.P. Kireev*, conceptualization, investigation, resources, data curation, writing original draft preparation; *I.A. Mandel*, investigation, resources, data curation, writing, review and editing; *T.V. Klypa*, conceptualization, visualization, data curation, supervision; *D.S. Sungurova,* investigation, resources, data curation; *I.M. Yanovskaya*, *A.N. Shepelyuk*, writing, review and editing. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The Anesthetic Management and the Specific Features of Perioperative Management in Cases of Nephrectomy with Thrombectomy From the Inferior Vena Cava in Patients with Renal Cell Cancer

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ABSTRACT

Renal cell cancer is one of the most widespread oncourological diseases (90% of all the malignant neoplasms in the kidneys) with high mortality. Every year worldwide, approximately 120,000 new cases of renal cell cancer are diagnosed, which is approximately 2% within the structure of the cancer incidence rates, and 65% of the patients are being diagnosed in the developed countries. Nephrectomy is the main method of radical therapy for such patients. In cases of tumor thrombosis of the inferior vena cava, which develops in 25–30% of the cases of renal cell cancer and represents a lethal complication of this disease due to the fragmentation of the thrombotic masses and developing pulmonary embolism, nephrectomy with thrombectomy is indicated. A special category includes the patients with renal cell cancer, complicated by the tumor thrombosis of the inferior vena cava with grades III (thrombus located at the level or above the hepatic veins, but below the diaphragm) and IV (thrombus spreading into the supradiaphragmatic inferior vena cava or into the right atrium) according to the classification by the Mayo Clinic, in which the surgical strategy is accompanied by significantly traumatic manipulations with the liver, the suprahepatic segment of the inferior vena cava, as well as with the heart chambers, suggesting the parallel cardiosurgical intervention. Surgical interventions with this background are accompanied by the complete or the parallel methods of extracorporeal circulation. The initially burdened status of the patient (tumor-related intoxication, anemia, hyperazotemia, in a number of cases thrombosis of the venous system in the lower limbs along with the concomitant abnormalities) and the extent of surgical intervention determine the high risk of complications (up to 93%) and hospital mortality (up to 10%). The preoperative evaluation of the risks of surgery, defining the most favorable tactics for the patient and the thorough preoperative preparation are necessary for the safest course of surgery and for the early rehabilitation of the patient. Currently, there is no unified commonly accepted algorithm adopted for managing such patients, while the developed commonly available standards often have a generalized type, not reflecting the specific features found in the patients with tumor thrombosis of the inferior vena cava. This review attempts to compile the specific features of the anesthetic management in cases of nephrectomy with thrombectomy in patients with renal cell cancer, to describe the main pathophysiological features of the tumor thrombosis of the inferior vena cava, the complications of the perioperative period, the methods for their prevention and treatment. The main directions were provided for the combined diagnostics and treatment, special attention was paid to the multi-disciplinary (urologists, oncologists, cardiovascular and cardiosurgery specialists, anesthesiologists and intensivists) team-based approach to perioperative management of the patients with tumor thrombosis of the inferior vena cava.

Keywords: *tumor thrombosis; kidney cancer; anesthetic care.*

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Анестезиологическое обеспечение и особенности периоперационного ведения при нефрэктомии с тромбэктомией из нижней полой вены у пациентов с почечно-клеточным раком

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АННОТАЦИЯ

Почечно-клеточный рак — одно из наиболее распространённых онкоурологических заболеваний (90% всех злокачественных новообразований почки) с высокой смертностью. Ежегодно в мире выявляют около 120 000 новых случаев почечно-клеточного рака, что составляет около 2% в структуре онкологической заболеваемости, 65% больных выявляют в развитых странах. Нефрэктомия является основным методом радикального лечения пациентов. При опухолевом тромбозе нижней полой вены, который развивается в 25–30% случаев почечно-клеточного рака и является смертельным осложнением данного заболевания в результате фрагментации тромботических масс и развития лёгочной эмболии, показана нефрэктомия с тромбэктомией. Особую категорию составляют пациенты с почечно-клеточным раком, осложнённым опухолевым тромбозом нижней полой вены III (тромб на уровне или выше печёночных вен, но ниже диафрагмы) и IV (тромб распространяется в наддиафрагмальную нижнюю полую вену или правое предсердие) уровня по классификации клиники Мейо, у которых хирургическая стратегия сопровождается значительными травматичными манипуляциями на печени, в надпечёночном отделе нижней полой вены, а также камерах сердца, предполагающими параллельное кардиохирургическое вмешательство. Оперативные вмешательства при этом сопровождаются полным или параллельным методом экстракорпорального кровообращения. Исходно отягощённое состояние пациента (раковая интоксикация, анемия, гиперазотемия, в ряде случаев тромбоз венозной системы нижних конечностей наряду с сопутствующей патологией) и объём хирургического вмешательства определяют высокий риск осложнений (до 93%) и госпитальной летальности (до 10%). Предоперационная оценка рисков операции, определение наиболее благоприятной для пациента тактики, тщательная предоперационная подготовка необходимы для наиболее безопасного выполнения операции и ранней реабилитации пациента. В настоящее время не существует единого общепринятого алгоритма ведения таких пациентов, а разработанные общедоступные стандарты носят зачастую обобщённый характер, не отражающий особенности пациентов с опухолевым тромбозом нижней полой вены. В обзоре предпринята попытка компилировать особенности анестезиологического обеспечения нефрэктомии с тромбэктомией у пациентов с почечно-клеточным раком, описать основные патофизиологические особенности опухолевого тромбоза нижней полой вены, осложнения периоперационного периода, способы их профилактики и лечения. Представлены основные направления комплексной диагностики и лечения, уделено особое внимание мультидисциплинарному (урологи, онкологи, сердечно-сосудистые и кардиохирурги, анестезиологи и реаниматологи) командному подходу к периоперационному ведению пациентов с опухолевым тромбозом нижней полой вены.

Ключевые слова: *опухолевый тромбоз; рак почки; анестезиологическое обеспечение.*

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INTRODUCTION

Renal cell cancer takes the second place by the incidence rate among the malignant neoplasms of the urogenital system, being in the top ten (4.9%) of the most commonly diagnosed malignant neoplasms in Russia. In 2023, there were 21,548 newly diagnosed cases of malignant kidney neoplasms, and the standardized morbidity rate for renal cell cancer was 10.14 per 100.000 of population [1]. Up to 25–30% of the cases of renal cell cancer are complicated by the tumor thrombosis of the renal vein and of the inferior vena cava, which in 1% of the cases reaches the right atrium [2].

The choice of surgical intervention in the treatment of renal cell cancer with tumor thrombosis of the inferior vena cava (TT IVC) depends mostly on the thrombus location level and, generally, includes the radical nephrectomy with the thrombectomy from the inferior vena cava (IVC) [3].

According to the classification by the Mayo Clinic, four levels of TT IVC are taken into account: level 0, in which the thrombus is limited by the renal vein; level I — the thrombus is spreading to the IVC by not more than 2 cm above the level of the renal vein; level II — the thrombus is spreading to the IVC by more than 2 cm above the level of the renal vein, but not reaching the level of hepatic veins; level III — the thrombus is at the level of the hepatic veins or higher, but below the diaphragm; level IV — the thrombus is spreading into the supradiaphragmatic IVC or into the right atrium.

Surgical interventions, especially in cases of level III or IV tumor thrombosis according to the Mayo classification, are technically complex and accompanied by the high risk of complications at all the stages of examination and therapy [4, 5]. In recent years, thanks to the constant enhancements of surgical approaches and of the instrumental basis, as well as due to the usage of artificial intelligence technologies, the radical methods of nephrectomy with IVC thrombectomy become more accessible and safer, however, the levels of complications and hospital mortality rates still remain high [6–8].

In the modern literature, the experience of anesthetic management and perioperative management for this cohort of patients is represented by predominantly single case reports or case series. Currently, there is no unified and commonly accepted algorithm for managing such patients [5, 9–17]. Systemizing the modern knowledge on the anesthetic approaches, the peri- and intraoperative risks, the methods of prevention, the timely diagnostics and treatment is necessary for increasing the survival rate and for improving the quality of the patients' lives [18].

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS OF TUMOR THROMBOSIS

Tumor invasion into the venous lumen occurs via the enzymatic destruction of the components of the IVC wall, mediated mainly by metalloproteinases, produced by the tumor cells, by fibroblasts and macrophages, participating in the immune response to the tumor presence. The basis of the active growth of tumor thrombosis is the presence of proprietary blood supply in the intraluminal tumor masses. The surface of the intraluminal tumor is covered in fibrin, which often promotes to the formation of blood clots [19].

Generally, the disease manifests with macrohematuria and pain in the lumbar area. Often, the tumor thrombosis has a long-term asymptomatic course, manifesting in some cases with symptoms of venous hyperemia, such as the swelling of the lower limbs, varicocele, dilation of the veins in the anterior wall of the abdominal cavity and the Budd-Chiari syndrome. The clinical signs of IVC obstruction are found quite rarely due to the development of collateral circulation. TT IVC levels III–IV may induce a short-term loss of consciousness, shortness of breath (upon the flotation in the right atrioventricular foramen) and the impairment of the cardiac rhythm. Some patients develop signs of chronic cardiac failure: tachycardia, shortness of breath, congestive signs in the lungs; the edematic syndrome can manifest as the cavity edemas, pastosity and swelling in the soft tissues. The relatively rare (0.9–2.4%) complication of TT IVC, related to the spontaneous fragmentation of the thrombus apex, is the pulmonary artery thromboembolism [20, 21].

ANESTHETIC MANAGEMENT

Preoperative preparation

For selecting the treatment tactics, a detailed information is needed on the spreading of the tumor process and on the functional reserves of the organism. For this purpose, before surgery, a pre-determined set of examinations is needed, requiring the involvement of the specialists of various profiles. TT IVC patients are characterized by an especially high risk of hemorrhages, hemodynamic instability with the development of hemodynamical complications in somatically compromised patients (classes III and IV of the Goldman scale), in which one can expect the development of myocardial infarction

types 1 and 2 [22], with this, it is expected that, the higher is the thrombosis level, the higher are these risks. In the patients of this cohort, clinically significant anemia is especially often diagnosed, requiring the preoperative correction and preparation of the reserves for intraoperative compensating the blood loss (donor erythrocyte suspension and fresh-frozen blood plasma, albumin solutions, the application of the equipment for the intraoperative blood re-infusion). Taking into consideration the high probability of intraoperative myocardial ischemia related to the hemodynamic instability and significant blood loss in the settings of possible coronary abnormalities, in such patients, it is practical to conduct the coronary angiography (CAG) for the purpose identifying or evaluating the dynamic changes of the stenoses in the coronary arteries. In case of detecting the significant lesions in the coronary circulation, re-vascularisation of the myocardium is to be performed [6, 23].

The risk of thromboembolic complications in TT IVC patients is especially high not only due to the fragmentation of the tumor thrombosis itself, but also due to the secondary thrombosis in the system of deep veins of the lower limbs. Before surgery and in the absence of contraindications, low molecular mass heparins are prescribed at the therapeutic dose. Due to the high risk of thrombus in-growth, routine installation of the cava-filter (a trap for the thrombi) should be avoided: the installation can be suggested in case of continuous episodes of pulmonary embolism, despite the use of anticoagulants, or in case of absolute contraindications to anticoagulant therapy. Other procedures include the ultrasound examination of the veins in the lower limbs for the purpose of diagnostics and evaluating the deep vein thrombosis [24–26].

All the patients with “high” (levels III and IV acc. to the Mayo classification) IVC thromboses, within the framework of the preoperative preparation, must obligatorily undergo echocardiography: such an examination allows for visualizing the thrombus head, for the dynamic detection of its mobility relative to the walls of the supradiaphragmatic segment of the IVC and the endocardium, the spreading of the thrombus from the right atrium into the ventricle, for evaluating the structure of the thrombus, as well as for non-invasively evaluating the pressure in the pulmonary artery [27].

One should also keep in mind the paraneoplastic toxic-anemic syndrome, related to the active oncology process, the hypovolemia and the impaired functions of the kidneys and of the liver. In particular, the depression of the renal functions can be caused by the decrease in the volume of the functioning parenchyma in cases of renal cell cancer (the course with signs of tubulointerstitial nephritis and canalicular necrosis) or tumor-associated blockage of the vein in the contralateral kidney. The tumor masses blocking the orifices of the main hepatic veins, lead to the increase of the venous pressure within the hepatic parenchyma, to the compression and stasis in the intrahepatic bile ducts and, as a result, to the impaired functions of hepatocytes [6]. The damage of hepatocytes resulting from the specific features of the liver blood supply, has the manifestations typical for hepatitis with signs of intoxication, decreased synthetic functions of the liver and coagulopathy, which aggravates the course of the oncological process.

According to clinical recommendations, patients with kidney cancer are advised to undergo laboratory examination at the extent of the clinical hematology panel (extended), the general clinical blood biochemistry panel, the extended panel of coagulation tests, the determination of the concentration of electrolytes (with paying attention to the levels of ionized and total calcium).

The patients, in which the use of intraoperative artificial circulation is planned, are recommended to undergo magnetic resonance tomography of the brain for the purpose of detecting the metastases that can lead to the intracerebral hemorrhage during the complete heparinization [27].

In case of chronic diseases, the preoperative period should include a consultation by the dedicated specialist with the determination of further follow-up tactics for the patient.

Intraoperative management of the patient

Combined and coupled anesthesia is used during the nephrectomy with IVC thrombectomy regardless of the thrombus location level. In case of level I–III thrombi, epidural anesthesia is also used at the level of Th7–Th8 as a component of multimodal analgesia, both in the intra- and in the postoperative period.

In case of level IV thromboses, the practicability of using epidural anesthesia remains disputable due to the high risk of developing the epidural hematoma caused by the necessity of complete heparinization during the artificial circulation. The role and the efficiency of high-level epidural anesthesia (Th2–Th5) for such interventions is not disclosed neither in the national nor in the foreign literature and it requires further research [28, 29], however, beyond question

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are its positive sides within the framework of improving the coronary circulation, the respiratory functions and the early rehabilitation after conducting the sternotomy. The technically correct conduction of this component of anesthetic support is considered safe [30, 31]. The reviews of the scientific literature on the problem of high epidural anesthesia in the settings of surgical interventions with using artificial circulation were not found in the accessible literature.

The optimal body temperature of the patient during nephrectomy with thrombectomy from the IVC still remains a discussible issue. Maintaining normothermia is necessary for the normal physiological functioning of the organs and for maintaining the function of blood clotting. It was proven that hypothermia and hypoperfusion increase the risk of perioperative hemorrhages and of the need for blood transfusions [17, 31] and, together with high risk of perioperative hemorrhages, induce the development of metabolic acidosis, which increases the coagulopathy and can become the reason of disseminated intravascular coagulation (DIC) syndrome. Maintaining the body temperature within the range of 36.5–37.4°C as the most comfortable is safe from the point of view of the possible development of complications related to unintended hypothermia. Intraoperative normothermia is assured by the use of convectional heating systems, of the flow-through thermostats with the constant control of the patient body temperature in the projection area of the lower third of the esophagus [28, 32]. A number of authors recommend maintaining the patient's temperature within the range of mild hypothermia, which, on their opinion, decreases the blood loss, for it decreases the aggregation of platelets and the activity of enzymes in the cascade reactions of blood clotting [33, 34].

As the intraoperative monitoring, the invasive/non-invasive measurement of blood pressure is used; as well as the electrocardiography, pulse oximetry, capnography and thermometry; other methods include the control of gases in the arterial blood and intraoperative thromboelastography, transesophageal echo-cardiography, intraoperative ultrasound examination, cerebral oximetry (INVOS technology) and the control of diuresis rate [6, 23, 28, 35].

Within the structure of the complications, the predominant one is the massive blood loss (up to 60%), which can induce hemorrhagic shock (0.9%) and acute coronary syndrome (0.3%) [6]. In case of massive blood loss, a practicability remains for the mechanical methods for auto-blood transfusions (Cell-Saver device) for the purpose of decreasing the transfusion burden with donor blood components and the complications related to it. Thrombectomy is often accompanied by significant variations of hemodynamics, which requires the active vasopressor support and infusion therapy [23].

One of the methods of conducting the surgical intervention in the settings of complete vascular isolation without the impaired hemodynamics is the artificial circulation, providing the hemodynamic stability and bloodless surgical field, and, hence, wider possibilities for revising and for the safety of surgical manipulations. The artificial circulation system also provides the possibility of compensating the intraoperative blood loss, of decreasing the need for allogenic blood transfusions [36, 37]. However, the method is accompanied by certain risks: systemic anticoagulation, coagulopathy, neurological complications and impaired functions of the kidneys affect the survival, the prognosis and the costs of hospitalization [4].

The traumaticity of the artificial circulation prompts to extremely selective choosing the candidates for conducting the procedure. Currently, a number of methods was suggested that allow for withdrawing from artificial circulation: the technique of venous-venous stenting, the milking (pressing out), the dislocation of thrombus using the Foley catheter etc. [5, 9, 13, 38–40], however, the fixated thrombi of levels III–IV, the predicted massive hemorrhage, the hemodynamic instability, the floating thrombi with high risk of fragmentation remain, according to the opinion of many investigators, an indication for implementing the artificial circulation [36, 37].

For preventing the formation of thrombi within the pipelines of the artificial circulation equipment, it is necessary to constantly control the time of active blood clotting, the minimal safe value for which is 400 seconds. The other "side of the coin" — the massive hemorrhage caused by the total heparinization of the organism — is also a life-threatening complication of artificial circulation. The contact of blood with air and tissues, the foaming and the introduction of foreign particles promote the activation of systemic inflammatory response, the coagulation cascade and the fibrinolysis, which also hampers the hemostasis [41].

The aspiration of the large volume of blood from the IVC into the pipelines of the artificial circulation equipment and the unintended hemodilution create the opportunities for developing the organ

dysfunctions. The damaging of the blood cells upon the aspiration and upon the passage along the pipelines of the artificial circulation equipment may lead to the post-perfusion hemolysis, which in turn, can induce the acute kidney damage and the acute respiratory distress-syndrome. It was proven that the blood pressure decrease to less than 80 mm.Hg. is less traumatic for the blood cells, hence, maintaining the proper level of pressure drop decreases the probability of damaging the blood corpuscles [42]. Besides, it is possible to intraoperatively use the hemofiltration column and to administer the donor erythrocyte-containing medications into the pipelines of the artificial circulation equipment for the purpose of correcting the hypervolemia and severe anemia resulting from the hemodilution [43, 44].

For the prevention of acute kidney damage caused by using the artificial circulation equipment, it is important to maintain an adequate cardiac output, to suppress the spasm of kidney vessels, to decrease the need for oxygen by means of moderate cooling and to use diuretics according to indications [45, 46].

Also, the importance of intra-operative ultrasound examination should be noted, which provides the possibility of not only evaluating the length and the structure of the thrombus, but also of reflecting the changes upon the compression of the renal hilum, the presence/absence of thrombus fixation to the venous wall, as well as of evaluating the non-tumor vascular component of the thrombus.

Intraoperative transesophageal echocardiography right after the induction of anesthesia allows for actualizing the data on the location of the tumor thrombosis; for evaluating its fragility and adhesion, as well as the degree of contraction; for detailing the level of IVC compression and the volemic status of the patient [35, 47]. Besides, the method allows for correcting the tactics of anesthetic support, for defining the functional status of the myocardium, the presence of abnormalities and the degree of perfusion at the real-time mode, which is especially important for critical conditions in severe patients, also helping to select the optimal volemic load, to evaluate the pre- and the afterload, the status of the valvular structures in the heart at the real time mode, to adjust the anesthetic medications and to predict the possible complications [35, 47].

Postoperative management of the patient

In case of adequate hemostasis within the first hours after surgery, anticoagulation is initiated with low molecular mass heparins at the therapeutic dosage with taking into consideration the glomerular filtration rate. Low molecular mass heparins are the drug of choice with the recommended gradual transition to the oral anticoagulants and with the duration of anticoagulant therapy being 3–6 months. It is practicable to use the unfractionated heparins due to the more comfortable control of therapeutic anticoagulation using the active clotting time and the activated partial thromboplastin time at the early post-surgery period with further transition to oral anticoagulants [48].

Taking into consideration the severity of the conducted surgery, during the postoperative period a multicomponent intensive therapy is implemented for the main disease and for the occurring complications, as well as for the concomitant diseases: multi-modal analgesia (epidural anesthesia, blockades of nerve trunks and plexuses, small dosages of narcotic analgesics in combination with non-steroid anti-inflammatory drugs of predominantly central action), the rational antibacterial therapy, the correction of anemic syndrome and the symptomatic therapy.

The necessary procedures also include the echocardiography (especially in case of “high” tumor thromboses), the ultrasound duplex scanning of the veins in the lower limbs, the ultrasound examination of the abdominal cavity organs and of the retroperitoneal space (with detecting the circulation in the contralateral kidney, in the renal vein and in the IVC; with the evaluation of free fluid presence) not less frequent than 1 time a week after surgery.

COMPLICATIONS OF THE POSTOPERATIVE PERIOD

The rates of developing complications at the early post-surgery period after nephrectomy with IVC thrombectomy reach 93%. Surgical complications grade I according to the classification by Clavien-Dindo were reported in 6.8–10% of the patients, grade II — in 10–75%, grade III–V — in 11–22.3%. The mortality at the early post-surgery period is, generally, caused by the multi-organ insufficiency, by venous thromboembolic complications, by the myocardial infarction and infectious complications. The hospital mortality rates, according to the data from various authors, vary within the values of 3.3–10% [6–8].

The significant predictors of perioperative complications and of the postoperative mortality are acknowledged to be the age of the patient, the high degree of comorbidity, the preoperative intoxication syndrome and the high spreading degree of tumor

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thrombosis [6, 8, 49, 50]. The extent of surgical blood loss, the rates of transfusions, the rates of developing complications during the early postoperative period and the duration of hospitalization increase with the length of the thrombi [49].

Within the structure of the complications developing in the early postoperative period, the coagulopathies and the hemorrhages prevail (10.0–66.0%), followed by the complications on the side of the cardiovascular system (37.8–57.0%), by the functional organ insufficiency (0.7–53.9%), infectious complications (3.7–23.0%) and the pulmonary artery thromboembolism (3.0–6.8%) [6, 49, 51–54].

Complications caused by the impaired blood clotting

Coagulopathies, hypocoagulation or disseminated intravascular clotting syndrome, generally, develop in patients having a history of massive blood loss and they can become complicated by clinically significant anemia, by the development of hematomas and their further infecting, as well as by the acute cerebrovascular events of the hemorrhagic type. The control of hemostasis and hemodynamics, of the red blood parameters along with the competent and timely prescription of anticoagulant therapy allow for preventing the development of these conditions. Oftentimes, non-complicated coagulopathies may resolve in a conservative manner (hemostatic therapy), however, in a number of cases (up to 3%), repeated surgical intervention is required. In cases of acute impairment of the cerebral circulation, intensive therapy is arranged, according to the indications — followed by the craniotomy with draining the intracranial hematoma [6].

Venous thromboembolic complications, including the phlebothromboses, re-thrombosis of the IVC and pulmonary artery thromboembolism can be caused both by the local (for example, incomplete removal of tumor masses from the IVC, damaging the vascular wall) and the systemic (hypercoagulation, associated with impaired rheologic properties of the blood, slowed circulation with a background of limited mobility at the early post-surgery period) factors. The proven risk factors of developing the pulmonary embolism are the cardiac rhythm disorders, which emphasizes the significance of cardiac monitoring and of the correction of arrythmias.

Myocardial infarction at the early post-surgery period after nephrectomy with IVC thrombectomy is more characteristic for patients with atherosclerotic lesions in the coronary vessels, which determines the necessity of arranging the coronary angiography and, according to the indications, re-vascularization of the myocardium within the framework of the preoperative preparation [45].

Organ insufficiency

Nephrectomy with IVC thrombectomy, especially in cases of level III–IV thromboses, bear the high risk of developing the functional insufficiency in separate organs and systems, as well as the risk of multi-organ insufficiency syndrome at the early post-surgery period. Within the structure of such complications, the expectably predominant is the acute kidney damage (up to 53.9%), which, generally, with a greater or lesser severity degree develops during the first 24 hours after surgery. The acute kidney damage is far from always becoming an indication to the renal replacement therapy (according to the data from various authors, only in 1.0–3.9% of the cases). The pathogenesis of these complication is, most probably, based on the decreased volume of circulating blood, on the changes in the renal hemodynamics and on the decreased volume of the functioning renal parenchyma. Based on the this, intraoperatively and during the postoperative period, it is necessary to thoroughly control the urine color, the diuresis, the blood levels of creatinine, urea and electrolytes, as well as to timely and justifiably employ the necessary measures (increasing the volume of circulating blood, controlling and normalizing the hemodynamic parameters, arranging the diuretic therapy and, according to indications — renal replacement therapy) [6, 45, 52].

Cardiac insufficiency develops in an average of 7.1% of the patients, approximately in three (0–12) days after surgery. Generally, cardiac insufficiency is a component of the multi-organ insufficiency syndrome, with this, up to 1/4 of the patients having this component as a part of multi-organ insufficiency syndrome, decease within the In-Patient Department. The main measure of preventing this complication is the control of hemodynamic parameters, the correction of the volume of circulating blood and the adequate anticoagulant therapy [6].

The development of respiratory insufficiency, reported in 4.7–10% of the patients, is associated with postoperative pneumonia, sepsis, progressive cardiovascular insufficiency, in single cases with fulminant progression of pulmonary metastases [6].

Hepatic failure is being diagnosed in an average of 5.3% of all the observations. The impaired functions

of the liver can become the residual event, caused by the long-term impaired hepatic circulation. The laboratory parameters of hepatic dysfunction related to the obstruction of the IVC, persists for up to half a year after re-canalizing the hepatic veins and the IVC [54, 55]. In part, the impairment of the liver functions can be resulting from the intraoperative ischemia. Besides, oftentimes hepatic failure is accompanied by the acute kidney damage. The main approach to the correction of this condition is the infusion therapy [6].

Nephrectomy with IVC thrombectomy, being a long-term and complex surgical intervention, oftentimes (up to 10% of the cases) is characterized by the dynamic acute intestinal obstruction during the postoperative period. The diagnostics of this condition requires ruling out the mechanical reasons. In cases of confirmed functional etiology of the dynamic acute intestinal obstruction, the sufficient positive effect can be provided by the early mobilization of the patient, by pro-kinetic therapy, as well as by the treatment aimed at adequate analgesia, at restoring the volume of circulating blood and the hemodynamic balance, at decreasing the inflammation, at the decompression of the gastrointestinal tract and tube feeding [56].

CONCLUSION

The key tasks for the anesthesiologist-intensivist are the preoperative evaluation of the surgery and the anesthesiology risks, the intra- and postoperative risk of cardiovascular complications defined with the participation of specialists from the adjacent specialties, the treatment of anemic syndrome using various correction methods, the evaluation and correction of the nutritive status, the preparation of the patients, in which surgical treatment is planned, with the minimization of the possible complications for the safest course of surgery and for the maximally comfortable early rehabilitation.

At the present moment, the criteria for selecting the patients for carrying out this extremely traumatic surgical intervention — the nephrectomy with IVC thrombectomy — are not established, there are no standardized algorithms for preoperative preparation, for the intra- and postoperative managing the patients with renal cell cancer, complicated with tumor thrombosis of the inferior vena cava. Summarizing the experience of anesthetic management and intensive therapy with further standardization of the diagnostics, follow-up and conservative therapy protocols will allow for increasing the survival and the quality of life for this complex cohort of patients.

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Microcystic Macular Edema: Clinical Significance and Pathogenetic Mechanisms

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ABSTRACT

Microcystic macular edema represents a specific type of intraretinal cystic changes, localizing predominantly in the inner nuclear layer and detectable using the optical coherence tomography. Contrary to the classic concepts on the macular edema as a result of vascular permeability, microcystic macular edema is not accompanied by exudation and it is perceived as the manifestation of neuroglial dysfunction, often associated with the damaging of the optic nerve. Initially described in patients with multiple sclerosis, microcystic macular edema was subsequently detected in the wide spectrum of diseases, including glaucoma, neuromyelitis optica spectrum disorders, diabetic retinopathy, occlusion of the retinal veins, senile macular degeneration and epiretinal membranes. The key pathogenetic mechanisms are considered the retrograde transsynaptic degeneration of the ganglionic cells in the retina and the functional/structural damage of the Muller's cells, in particular, the impaired operation of the AQP4 aquaporin channels. The morphological features of the microcystic macular edema, its location and clinical significance vary depending on the main disease and in a number of cases can act as the early biomarker of the neurodegenerative process. The article contains the pathophysiological models, the clinical correlates and the modern methods of the diagnostics of microcystic macular edema with special emphasis on the role of multimodal visualization and artificial intelligence technologies. Taking into consideration the rates of accidental detection and the potential relation to the systemic diseases, microcystic macular edema should be considered not as an isolated ophthalmology condition, but as the component of wider neuroretinal disorder requiring interdisciplinary approach to the diagnostics and follow-up.

Keywords: *microcystic macular edema; Muller's cells; retinal neurodegeneration; optical coherence tomography; retrograde degeneration.*

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List of abbreviations

IR — infrared visualization
MME — microcystic macular edema
OCT — optical coherence tomography
AQP4 (Aquaporin-4) — aquaporin-4 (the protein of water channels encoded by the *AQP4* gene)
GCL — ganglion cell layer
INL — inner nuclear layer
RNFL — Retinal Nerve Fiber Layer
SCP — Superficial Capillary Plexus

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Микрокистозный макулярный отёк: клиническое значение и патогенетические механизмы

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АННОТАЦИЯ

Микрокистозный макулярный отёк представляет собой специфический тип интраретинальных кистозных изменений, локализующихся преимущественно во внутреннем ядерном слое и выявляемых с помощью оптической когерентной томографии. Вопреки классическим представлениям о макулярном отёке как следствии сосудистой проницаемости, микрокистозный макулярный отёк не сопровождается экссудацией и рассматривается как проявление нейроглиальной дисфункции, часто ассоциированной с поражением зрительного нерва. Первоначально описанный у пациентов с рассеянным склерозом микрокистозный макулярный отёк впоследствии был обнаружен при широком спектре патологий, включая глаукому, нейромиелит спектра AQP4, диабетическую ретинопатию, окклюзию вен сетчатки, возрастную макулярную дегенерацию и эпиретинальные мембраны. Ключевыми патогенетическими механизмами считают ретроградную транссинаптическую дегенерацию ганглиозных клеток сетчатки и функциональное/структурное нарушение клеток Мюллера, в частности нарушение работы аквапориновых каналов AQP4. Морфологические особенности микрокистозного макулярного отёка, его локализация и клиническое значение варьируют в зависимости от основного заболевания, а в ряде случаев могут служить ранним биомаркером нейродегенеративного процесса. В статье рассматриваются патофизиологические модели, клинические корреляты и современные методы диагностики микрокистозного макулярного отёка с особым акцентом на роль мультимодальной визуализации и технологий искусственного интеллекта. Учитывая частоту случайного выявления и потенциальную связь с системными заболеваниями, микрокистозный макулярный отёк следует рассматривать не как изолированное офтальмологическое состояние, а как компонент более широкой нейроретинальной патологии, требующей междисциплинарного подхода к диагностике и наблюдению.

Ключевые слова: *микрокистозный макулярный отёк; клетки Мюллера; ретинальная нейродегенерация; оптическая когерентная томография; ретроградная дегенерация.*

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INTRODUCTION

Microcystic macular edema (MME) represents a specific form of retinal disorder, characterized by the formation of clearly delimited cystous cavities, predominantly in the inner nuclear layer (INL) and detectable by means of optical coherence tomography (OCT) [1, 2]. Initially described by J.M. Gelfand et al. [3] in patients with multiple sclerosis and optic neuritis, MME was subsequently revealed in a number of ophthalmological and systemic diseases, including the optic neuropathies, the diabetic retinopathy, the epiretinal membranes and the neurodegenerative processes in the central nervous system [4–7].

Unlike the diabetic macular edema and the senile macular degeneration, MME is not associated with significant vascular or inflammatory disorders,

which allows for considering it an independent clinical-pathogenetic entity [8]. The most probable mechanisms of its development are considered the retrograde transsynaptic degeneration of the ganglionic cells and the dysfunction of the Muller's cells, however, their interrelation and the contribution in the clinical signs require further research [8].

MICROCYSTIC MACULAR EDEMA: GENERAL PROVISIONS

Pathogenetic mechanisms

The development of MME is related to several key pathogenetic mechanisms, the basic of which is believed to be the retrograde transsynaptic degeneration (table 1) [9–17]. Unlike the classical forms of macular edema, related to vascular permeability, in cases of MME, there is no exudation present, which is confirmed by the results of OCT and angiography [9–11].

Retrograde degeneration developing after the death of ganglionic cells and their axons is accompanied by the damage of the structure of bipolar neurons in the INL, which results in the development of intraretinal cavities [12–14]. A clear correlation is observed between the zones of visual field loss and the topography of cystous changes, which emphasizes the secondary (neurodegenerative) origin of MME.

The dysfunction of the Muller's cells is another significant factor of pathogenesis. These glial cells support the water-ion homeostasis of retina, including the use of aquaporin channels (Aquaporin-4, AQP4). The impairment of their functions, including the one developing under the effects of autoantibodies (for example, in cases of the neuromyelitis of the optic nerve), can lead to the intraretinal accumulation of fluid with no signs of vascular leak [11, 12, 15].

Mechanical impact — the vitreomacular traction — is perceived as an additional but not universal mechanism. Though the tension in the vitreous body can enhance the formation of cysts, it is not the obligatory condition for their development [16].

The possible additional link is the inflammatory component, especially in cases of multiple sclerosis, in which the internal retina can be involved into the subclinical inflammatory process [3, 17], however, the clear relation between the presence of MME and the activity of multiple sclerosis is not determined as of today.

Thus, MME represents a multifactorial phenomenon occurring with a background of axonal loss, glial dysfunction and possible participation of inflammation. The role of each of these components may vary depending on the main disease.

Specific features of visualization

MME manifests with hyporeflexive cystous structures, predominantly of parafoveal location, more often in the lower part of the INL, showing the shape of an arch or a crescent. These changes are well visualized upon the spectral OCT as the zones of local decrease in the reflectivity, corresponding to the intraretinal cavities [11]. According to the data from B. Wolf et al. [11], in the lower third of the cysts, hyperreflective inclusions can be found, especially in cases of optic nerve atrophy. OCT-tomography of the macular profile (face map) has shown the predominant location of cysts in the upper and nasal quadrants (72%), while in cases of multiple sclerosis, even distribution was observed [3, 11]. In the

Table 1

Pathogenetic mechanisms of microcystic changes in the macula in cases of optic nerve damage

Mechanism	Backbone of the mechanism	Sources	Note
Neurodegeneration	Atrophy of the axons and ganglionic cells in the retina, leading to secondary degeneration of INL	[9–11]	Main background mechanism
Vitreomacular traction	Mechanical effects on the vitreous body with the thinned retina after the death of ganglionic cells; leading to microschisis	[16]	Cause-and-effect relation not proven
Retrograde transsynaptic degeneration	Secondary degeneration of post-synaptic bipolar neurons in the INL after the death of ganglionic cells	[12–14]	The most probable main mechanism
Dysfunction of the Muller's cells	Impaired homeostasis of fluid and ions in the retina due to the damage or dysfunctions of the gliocytes (including AQP4)	[11, 12, 14]	Confirmed for ONM and hereditary opticopathies
Inflammatory mechanism (including the multiple sclerosis)	INL as a target for inflammation, especially in multiple sclerosis; MME may correlate with the neurological deficit	[3, 13, 17]	No univocal relation to the activity of inflammation

Note. ONM — neuromyelitis optica; MME — microcystic macular changes; INL — inner nuclear layer of retina; AQP4 — aquaporin-4.

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glaucoma-affected eyes, MME is more often detected in the lower hemisphere of the retina [18], which can reflect the topographic features of neurodegeneration in various forms of optic neuropathy.

Infrared (IR) visualization and red-free images allow for visualizing the characteristic arch- or ring-shaped obscuring caused by the diffraction with a background of cysts [14, 19]. Adaptive optics also reveals the oval hyporeflexive structures that indicate the degeneration of the INL cells [19].

Fluorescent angiography in the majority of cases does not reveal exudation, which confirms the non-vasogenic nature of MME [11], however, separate cases describe the diffuse leakage of fluorescein into the INL, indicating the probable partial impairment of the hematoretinal barrier [20].

Data from OCT-angiography supplement the pathophysiological findings: a correlation was found between MME and the disorders in the superficial capillary plexus (SCP), which can indicate the microvascular component of the pathogenesis [21].

Thus, the combined set of imaging methods (OCT, OCT-angiography, infrared visualization, adaptive optics) ensures the accurate diagnostics of MME and promotes to its differentiation from other forms of maculopathy (table 2) [3, 11, 18–21].

MICROCYSTIC MACULAR EDEMA IN CASE OF THE OPTIC NERVE DISORDERS

The MME is associated with a broad spectrum of optical neuropathies, both acquired and hereditary, including multiple sclerosis, optic neuritis, glaucoma, compression-related and ischemic forms, as well as the Leber's disease and the autosomal dominant optic atrophy (table 3) [1, 3, 6, 11–13, 17, 18, 20–36].

Multiple sclerosis

First described by J.M. Gelfand et al. [3], MME in multiple sclerosis occurs in 4.7–6.1% of the cases and is more associated with the preceding optic neuritis [3, 13]. Its presence correlates with the worse neurological parameters defined when using the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Severity Score (MSSS), as well as with the decrease of vision acuity and thickening of INL [13, 20, 22]. The main pathogenetic hypotheses include the inflammatory damage of INL, the retrograde transsynaptic degeneration and the glial dysfunction related to the autoantibodies to KIR4.1 (inwardly rectifying potassium channel) and AQP4 [17, 20]. With the progression of the disease, thinning is observed in the inner layers of retina along with the worsening of visual functions [23–25].

Neuromyelitis optica

The rate of developing MME in cases of optic neuritis reach 20–40% and, generally, it is limited to the eyes with past history of optic neuritis [3, 21, 26–29]. The pathogenesis includes autoimmune impairment of the Muller's cells via the AQP4-IgG and further glial dysfunction increasing the retrograde degeneration [28]. According to "two-hit" hypothesis [12],

Table 2

Specific visualization features in cases of microcystic macular changes

Visualization method	Characteristic findings	Source	Note
Spectral OCT	Hyporeflexive arch-shaped microcysts, predominantly in the lower part of INL	[11]	Reflecting the intraretinal cavities
OCT, face map profile	Predominant location in the upper and nasal quadrants (72%)	[11]	Variability of distribution in various diseases
OCT in multiple sclerosis	Even distribution of microcysts in the macula	[3]	Specific features in multiple sclerosis
OCT in glaucoma	Microcysts in the lower hemisphere of the retina	[18]	Possible locational susceptibility
IR-visualization, red-free filter	Obscuring, arch-shaped and ring-shaped structure	[14, 19]	Relate to the diffraction of IR-radiation
Adaptive optics	Oval-shaped hyporeflexive structures	[19]	Degeneration of the INL-cells
Fluorescent angiography	Absence of exudation, in some cases — moderate leakage	[11, 20]	Supporting the non-inflammatory nature of the MME
OCT-angiography	Impairment of SCP, correlation with MME	[21]	Role of microvascular changes

Note. OCT — optical coherence tomography; IR — infrared visualization; MME — microcystic macular changes; INL — inner nuclear layer or retina; SCP — superficial capillary plexus.

Table 3

Microcystic changes in the macular in various forms of optic neuropathy

Neuropathy type	Specific features of the MME	Proposed	Sources
Multiple sclerosis	MME in 4.7–6.1% of the patients were associated with episodes of ON, thickening of INL, impaired visual functions	Neuroinflammation, dysfunction of the Muller's cells, autoantibodies to KIR4.1 and AQP4	[3, 6, 13, 17, 20, 22–30]
Neuromyelitis optica	MME in 20–40% of the patients, specifically in the eyes with past optic neuritis, more expressed thinning of the RNFL and GCL	Antibodies to AQP4, glial dysfunction, retrograde degeneration, vascular impairments of the SCP	[3, 12, 21, 26–28]
Non-inflammatory optical neuropathy (ischemic, compression-related etc.)	MME in 8.8–20.4% of the eyes correspond to the zones of lost nerve fibers	Retrograde transsynaptic degeneration, vitreomacular traction	[12, 19, 30–32]
Hereditary optical neuropathy (ADOA, LHON)	Ring-shaped perifoveal distribution of cysts, matching with the zones of RNFL and GCL loss	Mitochondrial dysfunction, glial instability, vitreal traction	[19, 33, 34]
Non-arteritis anterior ischemic optical neuropathy	Transitory MME during the INL acute phase; in some cases — stable changes in several months	Impaired blood-brain barrier, dysfunction of the Muller's cells, glymphatic insufficiency	[12, 30, 35, 36]

Note. MME — microcystic macular edema; ON — optic neuritis; INL — inner nuclear layer; KIR4.1 — potassium channel, associated with Muller' cells; AQP4 — aquaporin-4; RNFL — retinal nerve fiber layer; GCL — ganglion cell layer; SCP — superficial capillary plexus; ADOA — autosomal dominant optical atrophy; LHON — Leber's disease.

the development of MME requires a combination of axonal loss and glial damage. Data from OCT-angiography show the presence of microvascular disorders in the SCP, which can reflect the additional vascular component of pathogenesis [21].

Other neuropathies

MME is also observed in cases of non-inflammatory optical neuropathies — ischemic, traumatic, compression-related or hereditary [6, 12, 30]. Histologically they are accompanied by degenerative INL cavitations with no signs of inflammation [31]. The spatial location of the cysts detected using the infrared visualization and adaptive optics corresponds to the zones of ganglionic cells density [32].

In cases of autosomal dominant optic atrophy and Leber's disease, MME is detected in 5–20% of the cases, predominantly in the perifoveal zone [19, 33]. It is suggested that vitreoretinal adhesion can enhance the cavitation of the retina with a background of mitochondrial insufficiency [12, 34].

In case of non-arteritic anterior ischemic optic neuropathy (NAION), transient "peripapillary MME" was described, resolving within one month, probably, due to the impaired hematoretinal barrier and glial dysfunction [30, 35, 36]. In a number of cases, classic MME was developing months after an acute episode, which corresponds to the pattern of transsynaptic degeneration [12].

Glaucoma

MME was first described in glaucoma patients as the manifestation of severe axonal loss [11]. According to the data from T. Hasegawa et al. [18], microcysts were detected in 6% of the patients with primary open-angle glaucoma, predominantly at the later stages of the disease. Their presence correlated with the localized defects of the retinal nerve fiber layer (RNFL) and with the thinning of the ganglion cell layer (GCL), while in cases of severe total decompensation (average deviation <15 dB) MME was not registered.

The mechanism of MME in glaucoma, besides retrograde degeneration, can include mechanical instability in the inner retinal layers with a background of RNFL/GCL thinning and INL tension [18]. According to N. Murata et al. [37], the occurrence rate of MME was 1.6%, with this, the surface area of the microcystic changes was related to the impaired central field of vision. J. Brazerol et al. [38] have also found the rate of 3% of the cases, supposing that the thinning of the ganglion layers is accompanied by compensatory thickening of the internal nuclear/external plexiform layers and the development of cysts designated as the manifestation of "retrograde maculopathy".

The research by K.I. Jung [39] has shown that the thickening of the INL can precede the formation of MME, acting as the early marker of glaucoma progression. Additionally, the variations of intraocular pressure can induce reactive gliosis of the Muller's

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cells, increasing their functional load and facilitating the development of cystous changes [39–42]. Despite this, G. Mahmoudinezhad et al. [43] did not confirm the presence of statistically significant association between MME and the rate of glaucoma progression, estimated by the mean deviation (MD) and by the visual field index (VFI). Nevertheless, the authors have noted the clear location of the retinal microcysts predominantly in the lower hemisphere of the retina (84%), which corresponds to the zone of typical glaucoma-related damage of the upper vision field [3, 44]. It was also noted that MME is not related to the epiretinal membranes, which rules out the vitreomacular traction as the leading mechanism [18, 44].

Thus, MME in glaucoma can be considered as the potential morphological marker of progressive central damaging of the optic tract, related to the glial dysfunction, to the local neurodegeneration and to the instability of inner retinal layers.

MICROCYSTIC MACULAR EDEMA IN CASES OF NEUROLOGICAL DISEASES

Microcystic changes in the retina are considered as the potential manifestation of transsynaptic retrograde degeneration in cases of disorders in the central nervous system. The research works confirm the degeneration of RNFL and GCL in patients with congenital abnormalities in the brain, with ischemic strokes and craniocerebral injuries, which is being associated with the loss of trophic support from the cortical neurons [45–47]. However, in single lesions of the posterior segments of the optic tract (for example, after hemispherectomy), MME was not found [48], which encouraged W.A. de Vries-Knoppert et al. [49] to differentiate the direct axonal and the transsynaptic degeneration. Only in cases of anterior impairment (chiasm, retrobulbar compression) the thinning of the retinal nerve fiber layer / ganglionic cell layer is registered with the inner plexiform layer and INL thickening along with the development of MME. The authors have isolated three types of degeneration [49] — the direct retrograde (the aggressive one with the development of MME), the local transsynaptic (restricted and slowly progressing) and the widespread transsynaptic (in cases of massive lesions, accompanied by axonal instability).

M.L. Monteiro et al. [50] have investigated 26 patients with chiasmal compression and found that MME is detected upon using the OCT in 35.3% of the eyes, while the hyporeflexive zones at the IR-image — in 64.7% of the cases. In total, signs of retrograde maculopathy were found in 58.8% of the eyes. Hyporeflexive foci were especially often detected in cases of striated atrophy, even in the absence of cysts in the OCT data, which emphasizes their diagnostic value in chronic disorders.

Thus, in cases of neurological disorders, no MME can be detected at the later phases, however, IR-visualization allows for revealing signs of retinal degeneration. This emphasizes the significance of the combined approach with using OCT and multispectral visualization for the evaluation of various stages of transsynaptic degeneration.

MICROCYSTIC MACULAR EDEMA IN CASES OF EPIRETINAL MEMBRANES

Epiretinal membranes may cause the development of intraretinal cysts, morphologically similar to MME, even in the absence of fluorescein leakage [51–54]. This calls into question their relation to the classical cystoid edema and allows for considering such changes as the manifestation of traction-related or retrograde maculopathy.

The research by A. Govetto et al. [16] has revealed MME in 55% of the patients with epiretinal membranes and glaucoma versus 11.3% of the patients without glaucoma. After vitrectomy, cysts were disappearing only in patients without glaucoma, which shows the role of retrograde component in the optic neuropathy. Mechanical tension of the epiretinal membranes can disrupt the functioning of the Muller's cells, blocking the reabsorption of fluid and stimulating the formation of cysts [55, 56].

The combination of epiretinal membranes and glaucoma increases the risk of MME [57]. Research works demonstrate both the regress of cysts after surgery and their repeated occurrence [56, 58, 59]. A number of authors relate these changes to the retrograde maculopathy triad — thinning of GCL, thickening of INL and formation of cysts [56]. However, the effect of MME on the vision prognosis remains disputable: some data show the absence of correlation, others show the worsening of outcomes in patients with significant MME and with an ectopy of the foveal layer [60].

Histologically, MME in case of epiretinal membranes is resulting predominantly from the mechanical damage of the Muller's cells, not from the neurodegeneration. MME is often detected with mature (stage III–IV) epiretinal membranes, but extremely rarely — in cases of macular holes [61], which confirms the role of chronic traction.

Thus, MME in cases of epiretinal membranes forms due to the mechanical destruction of glial cells, especially with a background of glaucoma, which requires taking it into consideration in the surgical tactics and when predicting the functional outcome.

Macular diseases

Water homeostasis of the retina is provided by a number of mechanisms, not depending on the hematoretinal barrier [8]. Excessive fluid may be produced even in the absence of inflammation or vascular leakage, which is caused by the absence of lymphatic system, by high metabolism in the photoreceptors and by the constant osmotic gradient between the vitreous body and the vascular membrane.

The removal of fluid is carried out by means of the activity of pigmented epithelium (retinal pigment epithelium, RPE), by the osmotic pressure of the choroid and by the functioning of the Muller's cells, which regulate the ion transport, absorb water and promote to its relocation to the choroid. These cells also affect the functioning of the retinal pigmented epithelium, including the regulation of the synthesis of vascular endothelial growth factor (VEGF) [62–64].

The macular zone is especially affected by the accumulation of fluid due to its high metabolic activity and the anatomic features, namely, the dense architecture, the adjacency to the premacular space and the fragile regulatory system relocating the fluid [65, 66].

In cases of abnormalities impairing the functioning of the Muller's cells (neurodegeneration, hypoxia, traction) or the pigmented epithelium (for example, in senile macular degeneration), non-exudative accumulation of fluid may develop, which form the basis of developing microcystic changes and other non-vasogenic forms of macular edema (table 4) [1, 8, 66–80].

Senile macular degeneration

Microcystoid lesions, morphologically similar to MME, may be detected at the later stages of both the atrophic and the exudative form of senile macular degeneration [8]. Among them, there are external retinal canaliculi, the subretinal transitory hyporeflexia and pseudocysts, developing mostly due to the degeneration of the Muller's cells. Such lesions do not show any leak upon fluorescent angiography and they are characterized by chronic course with a background of metabolic decompensation of neuroretina.

External retinal canaliculi represent the stable hyperreflexive structures in the external layers, unlike the regressing MME [66]. The subretinal transitory hyporeflexia, on the contrary, has a transient course and does not involve the internal layers [67]. Pseudocysts in geographic atrophy are registered in ~27% of the cases [68], with this, they are not associated with a risk

Table 4

Microcystic changes in the macula in cases of macular diseases and retinopathies

Disease	Type of changes	Characteristics and pathogenesis	Sources
Senile macular degeneration	Pseudocyst, ERC, STH	Degenerative non-vasogenic changes, not accompanied by exudation, related to the impaired functions of the RPE and the Muller's cells. Differ from the MME by the location and stability	[8, 66–70]
Diabetic retinopathy	PMC, thickening of INL	Early glial dysfunction, changes without exudation, more in the nasal and temporal quadrants. Precedes the classical DME	[1, 71, 72]
Retinal vein occlusion	MME	Often combined with glaucoma, associated with unfavorable prognosis. Resistant to therapy in cases of concomitant glaucoma	[73, 74]
Macular telangiectasis of type 2	Cystous changes	Early loss of the Muller's cells, degenerative mechanism, absence of response to anti-VEGF, possible development of secondary macular holes	[75–77]
Central serous chorioretinopathy	Degenerative cysts	Chronic form, no exudation, in the external layers of retina, often with pachychoroid changes	[78, 79]
Hereditary retinal dystrophies	Cystic changes	Reported in cases of various hereditary abnormalities, predominantly of degenerative nature, up to 30% without exudation	[80]

Note. ERC — external retinal canaliculi; STH — subretinal transitory hyporeflexia; PMC — pseudomicrocystic changes; DME — diabetic macular edema; MME — microcystic macular changes; RPE — retinal pigment epithelium; INL — inner nuclear layer; VEGF — vascular endothelial growth factor.

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of secondary exudation [69]. Degenerative cysts in cases of exudative senile macular degeneration can persist with a background of anti-VEGF therapy [70], however, they differ by the pathogenesis and they are not associated with neuroglial mechanisms.

Upon the development of diabetic retinopathy, MME with pseudomicrocystic changes occurs already at the early stages, before the development of vasculopathy. According to the data from R. Forte et al. [71], pseudomicrocystic changes were observed in 14% of the eyes with intact vision acuity, but with decreased photosensitivity. These changes are accompanied by thickening of the INL, which indicates the glial dysfunction before the development of macular edema [72].

The morphology of pseudomicrocystic changes in cases of diabetic retinopathy differs: the cysts are elongated, with blurred margins, localizing at the nasal and temporal quadrants of the macula. It is suggested that they reflect the hypoxia-induced impairment of the Muller's cells, enhanced by the impaired chorio-capillary perfusion [1].

Thus, in cases of senile macular degeneration, just like in the diabetic retinopathy, microcystic changes represent a result of various pathogenetic mechanisms — degenerative, hypoxic or glial. Their detection has a differential-diagnostic and prognostic value, especially at the early stages of the disease.

Retinal vein occlusion

MME often occurs after the retinal vein occlusion, especially in the untreated cases. According to the data from the retrospective research by A. Francone et al. [73], MME was detected approximately in 70% of the eyes with retinal vein occlusion. Notably, the concomitant glaucoma was a significant risk factor of developing MME in cases of retinal vein occlusion. In the eyes with combined disease (retinal vein occlusion + glaucoma), there was a larger number of cystoid cavities and a more significant decrease of the best corrected vision acuity comparing to the isolated retinal vein occlusion. After the anti-VEGF therapy, MME persisted in 44% of the cases when combined with glaucoma, while in the isolated retinal vein occlusion — only in 15%. However, even in the latter group, the presence of MME was associated with increased risk of edema recurrence, of the shortening inter-interval period between the injections and the necessity of longer supportive therapy [74].

The obtained data emphasize that MME in cases of retinal vein occlusion can be considered a marker of unfavorable functional prognosis, especially in the settings of glaucoma-related optic neuropathy, where the glial mechanisms of compensating the hydration balance are initially abnormal.

Other diseases

Macular telangiectasis type 2 is characterized by early cystous changes in the inner layers of retina and by whitening of the parafovea. Histologically confirmed reduction of the Muller's cells indicates their central role in the pathogenesis. The progression is accompanied by the degeneration of the external layers and of the photoreceptors, as well as by the risk of developing the secondary lamellar macular hole [75, 76]. Anti-VEGF therapy is ineffective and it can aggravate the atrophic changes [77].

Central serous chorioretinopathy in its chronic form may be accompanied by cystoid lesions with no signs of leakage, predominantly in the external layers of retina. Such changes are often resistant to the therapy and are associated with pachychoroid morphology [78, 79].

Hereditary retinal dystrophy, including the S-cone syndrome, the Best disease and the pigmented retinitis, are also accompanied by microcystic changes. In part of the patients (up to 30%), the cysts are not detectable when using the fluorescent angiography, which confirms their degenerative nature [80].

Thus, MME can be found in a wide spectrum of diseases — from vascular to hereditary, reflecting the universal mechanisms of glial dysfunction or of the structural depletion of neuroretina.

DISCUSSION

MME represents a phenotypically recognizable but pathogenetically heterogeneous condition occurring during multiple ophthalmology and systemic diseases. Modern data indicate that the development of MME is the result of several interacting pathophysiological mechanisms, including the neurodegeneration, the glial dysfunction and the impairment of water homeostasis. Though most commonly MME is associated with chronic disease of the optic nerve, its presence was also documented in cases of senile macular degeneration, diabetic retinopathy and retinal vein occlusion.

Retrograde transsynaptic degeneration is traditionally concerned as a central pathogenetic mechanism, especially during the neurodegenerative diseases of the optic tract, however, mounting evidence underlines the key role of the dysfunction of the Muller's cells, the glial elements of retina, responsible for water-ion balance and the structural support of

the inner retina [31, 81]. Specifically — in recent years, the participation of AQP4 channels, expressed by the Muller's cells, gains more attention. Their functional incompetence, mediated by the autoantibodies in cases of optic neuromyelitis, results in the impaired transcellular water transport and the development of MME. At the same time, there are data that indicate the more multi-purpose role of AQP4 in the development of MME, including cases of multiple sclerosis. The interaction of AQP4 with Kir4.1 Potassium channels, also expressed by the Muller's cells, maintain the osmotic balance in the retina. The impairment of the combined regulation of these channels lead to the decreased resorption of fluid and to the development of the intra-retinal cysts [1, 16].

The additional role in the impaired functions of the Muller's cells can be played by the mechanical damage, especially in cases of epiretinal membranes. Research works have demonstrated that delamination of INL during the surgery for epiretinal membranes can aggravate the damage of glial cells, resulting in the increased rates of postoperative MME [61]. Thus, the unifying link for the multitude of various diseases is the impairment of the functional or structural integrity of the Muller's cells, which results in the dysregulation of AQP4 and water homeostasis.

Separate attention deserves the topography of microcystic changes, which are in many cases localized predominantly at the nasal and temporal quadrants of the perimacular area. Such selectivity can be resulting from the specific anatomical features of the vascular system of the choroid, in particular, the watershed areas between the basins of posterior ciliary arteries located between the central fovea and the optic nerve disc. These zones can be more vulnerable to hypoxic or ischemic effects [82].

Interesting observation is the registration of hyperreflexive inclusions in the macular zone in patients with senile macular degeneration and diabetic retinopathy, which can represent the activated microglial cells. This indicates the probable involvement of the inflammatory cascades at the early stages of degenerative and vascular retinal diseases, predisposing to the development of MME [83].

Despite the clearly defined morphological characteristics, clinical significance of MME remains a matter of discussion. The MME is not always accompanied by impaired vision acuity, especially at the early stages, however, in patients with multiple sclerosis and senile macular degeneration, the presence of MME was associated with the worsening of the functional parameters and with the decreased sensitivity of the retina [3, 13, 28]. At the same time, in cases of myelitis, such associations are less clearly trackable, while the intensity of MME does not correlate with the total level of neurological incapacitation.

Thus, MME should be estimated not as an independent nosological entity, but as a morphological marker of neuroglial balance destabilization at the macular zone. Its detection can act as an alarm signal both for the ophthalmologists and for the neurologists, pointing out the necessity of deeper structural and systemic examination arranged for the patient.

CONCLUSION

Microcystic macular edema represents a non-specific manifestation of impaired water homeostasis in the retina, associated predominantly with the dysfunction of the Muller's cells and retrograde neurodegeneration, observed in a wide spectrum of diseases — from the damage of the optic tract to the vascular, degenerative and hereditary retinopathies, which requires accurate differential diagnostics. Due to the presence of modern visualization methods, MME gains the value as an important morphological marker, capable of indicating an occult disorder, which emphasizes the clinical-diagnostic value of MME and the necessity of further cross-disciplinary research.

ADDITIONAL INFORMATION

Author contribution: *E.A. Danilova,* conceptualization, literature search and analysis, data processing, manuscript writing; *I.V. Plokhikh*, *L.M. Dzhanbekova,* conceptualization, literature analysis, data processing, manuscript editing; *A.E. Tyan*, *G.I. Nafikova*, *G.I. Antipina,* discussion and interpretation of data, manuscript editing; *A.I. Bikbulatova*, *Yu.A. Rybina*, *M.S. Khulagov*, *M.I. Batdyeva,* data discussion; *K.M. Gaifullina*, *I.V. Vasilieva*, *A.E. Krivosheeva*, *I.A. Usmanov,* participation in manuscript preparation and approval of the final version. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Differential Diagnostics of Non-Small-Cell and Small-Cell Lung Cancer: Modern Approaches and Promising Technologies

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ABSTRACT

Lung cancer represents a heterogeneous group of malignant neoplasms, among which two main forms can be distinguished — the non-small-cell and the small-cell lung cancer. These subtypes significantly differ by the histological, the molecular-genetic and the clinical characteristics, which defines the necessity of precise differential diagnostics for selecting the optimal treatment tactics. The review highlights the modern methods of diagnostics for the non-small-cell and the small-cell lung cancer, including the instrumental diagnostics, the histological and immunohistochemical examinations. Special attention was paid to the pros and cons of the promising non- and minimally invasive approaches, such as the analysis of circulating tumor cells, of the extracellular DNA, of the miRNA, of the marker proteins, of the volatile organic compounds and of the modern medical visualization (radiomics). Despite the significant progress in developing new diagnostic approaches, the problems remain that are related to the heterogeneity of tumors, the limited accessibility of the materials of small-cell lung cancer and the necessity of standardizing the new methods. The promising direction seems to the integration of multimodal approaches, combining the fluid biopsy, radiomics and the algorithms of machine learning, which can increase the precision of diagnostics and optimize the personalized treatment of the patients with various subtypes of lung cancer.

Keywords: *non-small-cell lung cancer; small-cell lung cancer; differential diagnostics; fluid biopsy; radiomics.*

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List of abbreviations

IHC — immunohistochemical examination
CT — computed tomography
VOC — volatile organic compounds
SCLC — small-cell lung cancer
NSCLC — non-small-cell lung cancer
PCR — polymerase chain reaction
PET-CT — positron-emission tomography, combined with computed tomography
LC — lung cancer
CTC — circulating tumor cells
FDA — USA Food and Drug Administration
NGS — next generation sequencing

INTRODUCTION

Lung cancer (LC) is a heterogeneous group of malignant neoplasms that differ by the histogenesis, the molecular-genetic profile, the clinical course and the treatment approaches. The source of tumor growth is the cells of the surface epithelium of bronchial mucosa, the mucosa of the bronchiolar glands and the pulmonary alveoli [1]. As for the mortality, LC takes the first place among men and second — among women both in Russia and worldwide; as for the incidence rates — also the first place among men, among women — the second and the fifth worldwide and in Russia, respectively [2, 3]. In total, LC remains the main cause of cancer-related death with the approximate

Дифференциальная диагностика немелкоклеточного и мелкоклеточного рака лёгкого: современные подходы и перспективные технологии

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АННОТАЦИЯ

Рак лёгкого представляет собой гетерогенную группу злокачественных новообразований, среди которых выделяют две основные формы — немелкоклеточный и мелкоклеточный рак лёгкого. Эти подтипы существенно различаются по гистологическим, молекулярно-генетическим и клиническим характеристикам, что определяет необходимость точной дифференциальной диагностики для выбора оптимальной тактики лечения. В обзоре рассматриваются современные методы диагностики немелкоклеточного и мелкоклеточного рака лёгкого, включая инструментальную диагностику, гистологическое и иммуногистохимическое исследование. Особое внимание уделено плюсам и минусам перспективных не- и малоинвазивных подходов, таких как анализ циркулирующих опухолевых клеток, внеклеточной ДНК, микроРНК, белковых маркеров, летучих органических соединений, современной медицинской визуализации (радиомики). Несмотря на значительные успехи в разработке новых диагностических подходов, сохраняются проблемы, связанные с гетерогенностью опухолей, ограниченной доступностью материала мелкоклеточного рака лёгкого и необходимостью стандартизации новых методов. Перспективным направлением представляется интеграция мультимодальных подходов, сочетающих жидкостную биопсию, радиомику и алгоритмы машинного обучения, что может повысить точность диагностики и оптимизировать персонализированное лечение пациентов с различными подтипами рака лёгкого.

Ключевые слова: *немелкоклеточный рак лёгкого; мелкоклеточный рак лёгкого; дифференциальная диагностика; жидкостная биопсия; радиомика.*

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statistics of 2.48 mln of new cases and 1.84 mln of fatal outcomes annually [3], despite the decrease in LC mortality in general within the last 10 years [4]. Though the incidence of LC among men is higher than among women, two tendencies were simultaneously observed — the decrease among men and the increase among women [5]. The decrease of the incidence among men is directly related to the decease in the rates of smoking, at the same time, the incidence in women gets increased to a greater extent among the non-smokers and at the age older than 60 years [6]. Women are more prone to the development of LC, not related to smoking, which the investigators associate with the intersexual differences of the rates of mutations in the epidermal growth factor receptor, in the anaplastic lymphoma kinase and in the Kirsten rat sarcoma homologue gene (*Kirsten rat sarcoma, KRAS*) [7, 8].

CLASSIFICATION OF LUNG CANCER

The classification of LC is based on the histological type of tumor and has the fundamental value for the diagnostics, the prognosis and the choice of treatment tactics. In the international clinical practice, the most widely used classification is the one from the World Health Organization along with dividing LC into two main groups: the non-small-cell lung cancer (NSCLC), which includes the most widespread adenocarcinoma, as well as the squamous and the large cell subtypes, as well as the small-cell lung cancer (SCLC), Fig. 1 [9].

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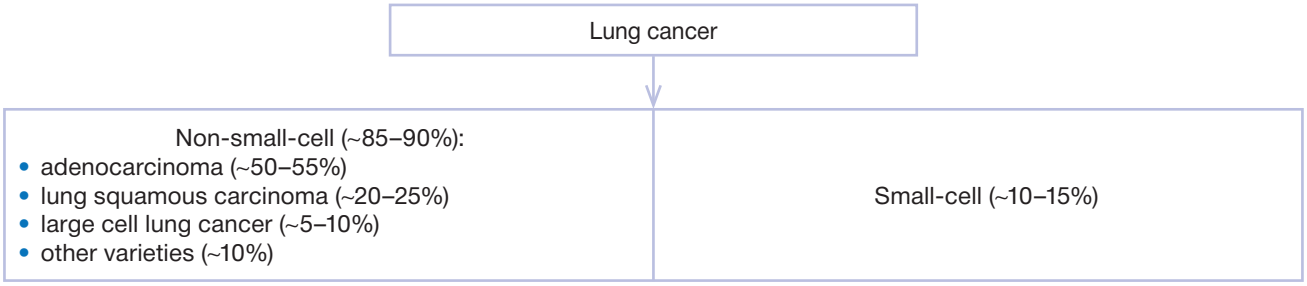

Fig. 1. Classification of lung cancer [8].

SCLC and NSCLC significantly differ by the origin, by the interrelation with smoking, by the course, the prognosis and the effective treatment (table 1)[1, 2] [1, 2, 10–22].

[1] National Cancer Institute [Internet]. *Cancer Stat Facts: lung and bronchus cancer*. Available at: https://seer.cancer.gov/statfacts/html/lungb.html

[2] American Cancer Society [Internet]. *Lung cancer survival rates*. Available at: https://www.cancer.org/cancer/types/lung-cancer/detection-diagnosis-staging/survival-rates.html

SCLC is an aggressive and rapidly growing tumor, often metastasizing into the liver, the brain and the bones, also, despite the initially reported sensitivity to chemo- and radiotherapy, frequently and rapidly developing the resistance with further development of recurrences. Within this context, the timely differential diagnostics of NSCLC and SCLC is an important task for the modern Medicine.

Table 1

Non-small-cell and small-cell lung cancer: key differences

Parameter	NSCLC	SCLC	Source
Incidence rate	86–89% — in males 90–93% — in females	11–14% — in males 7–10% — in females	[10, 11]
Origin	Adenocarcinoma — glandular cells producing the mucus. Squamous carcinoma — epithelial cells	Neuroendocrine cells of the basal epithelium in the bronchi	[1, 12, 13]
Location and features	More commonly seen in the peripheral zone (especially adenocarcinoma), less frequently — in the central one (more often — squamous carcinoma). The tumor cells have signs of malignant transformation of the epithelium	Central tumor, developing from the submucosal layers of the airways as the perihilar mass. The cells appear as the spindle-like or round cells with sparse cytoplasm, grained chromatin, necrosis is often found	[12–14]
Relation to smoking	~84% of the cases (adenocarcinoma can develop in non-smokers)	>96% of the cases	[15]
Subtypes	Adenocarcinoma, squamous, large cell	Pure SCLC, combined (with elements of NSCLC)	[1]
Typical mutations	*EGFR, KRAS, ALK, ROS1*	Loss of TP53 and RB1	[16–21]
Course	Slow growth, late metastatic activity	Aggressive growth, early metastatic activity (into the brain and liver)	[1]
Treatment	Surgery — at early stages. Chemotherapy — at stages II, III and in some cases — at the B stage. Radiation therapy. Target therapy (inhibitors of EGFR, ALK). Immunotherapy (PD-1/PD-L1)	Surgical treatment is rarely used due to the early metastatic spreading, only for stage I (IA and IB) and in separate cases at the stage II with an obligatory adjuvant chemotherapy. Systemic chemotherapy (etoposide + platinum) + immunotherapy (Atezolizumab) + radiotherapy (optional). Rapid development of resistance to chemotherapy (often related to the loss of TP53/RB1)	[2, 13]
Prognosis	Better (five-years survival rate ~32% in total for all the stages)	Worse (five-years survival rate <9% in total for all the stages)	-
Paraneoplastic syndromes	Rare	Often (SIADH, Cushing syndrome)	[22]

Note. NSCLC/SCLC — non-small-cell/small-cell lung cancer. SIADH — syndrome of inappropriate antidiuretic hormone secretion.

DIFFERENTIAL DIAGNOSTICS OF NON-SMALL-CELL AND SMALL-CELL LUNG CANCER IN THE SETTINGS OF MODERN CLINICS

In the modern clinical practice, the differential diagnostics of SCLC and NSCLC is arranged in a combined manner using the methods of radiography, computed tomography (CT), positron-emission tomography combined with the computed one (PET-CT), bronchology examination with further histological and immunohistochemical diagnostics (the main method), as well as the method of molecular-genetic testing for NSCLC (Fig. 2). The clinical indications for conducting these examinations include such symptoms as coughing, difficulty of respiration, shortness of breath, chest pain, rales, blood spitting, weakness, fatigability, decreased appetite, frequent infections of the chest cavity organs, constant pain in the chest or shoulders, hoarseness or depression of voice and the unexplainable loss of body weight [2, 13].

Methods of diagnostic visualization

The methods of diagnostic visualization include the radiography, the CT and the PET-CT. The chest cavity radiography is not recommended as the population screening of LC, for the prospective randomized research works did not reveal a significant decrease in LC-related mortality when using this method as the screening one. The sensitivity of radiography for detecting the early stages of LC is less than 50%, which is why, when suspecting the presence of tumor, CT is obligatory, however, radiography is still the main method of detecting the primary evidences of LC with the present clinical indications. For the purpose of further evaluating the pathological changes revealed using the radiography, CT examination is used with intravenous bolus contrasting [2].

Though the exact subtype of LC is impossible to detect using CT, nevertheless, there are indirect signs characteristic for SCLC, which include the central location of tumor with massive mediastinal lymphadenopathy, as well as the rapid growth and early metastatic activity. At the same time, NSCLC can be both the peripheral (adenocarcinoma) and the central (squamous), and, generally, it progresses at a slower rate.

The evaluation of the metabolic activity using the radiopharmaceutical (usually the radio-labeled glucose analogue, into the molecules of which, the radioactive fluoride-18 isotope is introduced (18F-FDG)) is based on the property of malignant tumors to actively absorb glucose, which helps differentiating them from benign changes (granulomas and scars). The sensitivity of PET-CT in detecting the malignant nodes is >90%, with the specificity of 70–85% (false-positive results are possible in cases of inflammation or infections). This method allows for staging the tumor process, classifying them using the TNM system (International classification of stages for malignant neoplasms: Tumor — tumor, Nodus — lymph nodes, Metastasis — metastases), detecting the metastases, with this, SCLC usually demonstrates a high SUVmax (maximal ^{18}F-FDG uptake coefficient) comparing to the NSCLC. The additional benefit of precise defining the tumor margins using the PET-CT is the possibility to optimize the exposure dosage and, as a result, to minimize the damage of healthy tissues.

Bronchological examination

Bronchological examinations, such as bronchoscopy and endobronchial ultrasound examination, are assigned as the main and the obligatory methods of LC diagnostics, which allow for not only visually examining the throat, the trachea and all the bronchi, for directly

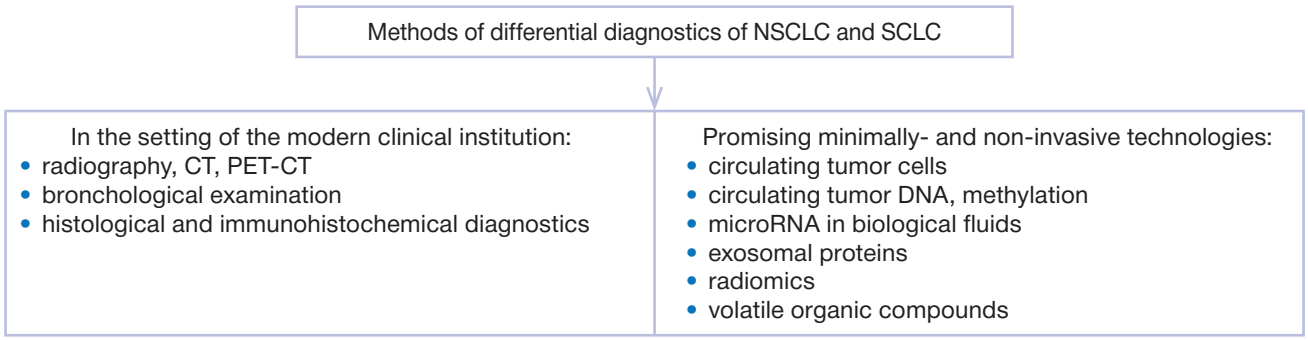

Fig. 2. The methods of differential diagnostics of non-small-cell and small-cell lung cancer. NSCLC/SCLC — non-small-cell/small-cell lung cancer; CT — computed tomography; PET-CT — positron-emission tomography, combined with computed tomography.

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observing the location of the tumor, for defining the margins of its spreading, for indirectly judging on the enlargement of the lymph nodes in the root of the lung and the mediastinum, but also for conducting the biopsy for histological examination (fine-needle and trephine biopsy), for obtaining the material (brush-bioptates, histological biopsy, impression smears, scrapings or washings from the bronchial tree) for further assessment. However, bronchoscopy has substantial limitations in the diagnostics of pre-cancerous lesions, for they are difficult to detect visually, as they consist of several layers of cells with a thickness of 0.2–1 mm and with a diameter of several millimeters [2, 12, 13].

Histological and immunohistochemical diagnostics

Histological and immunohistochemical (IHC) diagnostics is the main method of modern differential diagnostics for NSCLC and SCLC. The histological criteria for SCLC include the small cells (measuring ~2–3 lymphocyte diameters), the small-grained pattern of chromatin in the cell nucleus ("salt and pepper"), the nuclear molding, the specific IHC-markers (CD56, Synaptophysin, Chromogranin A — neuroendocrine differentiation), as well as the frequent loss of *RB1* and *TP53* genes (detected using the molecular-genetic methods).

The criteria for NSCLC include the following: large cells with clear cytoplasm and IHC-markers [adenocarcinoma: TTF-1, Napsin A; squamous: p40 (more specific), p63, CK5/6].

Molecular-genetic testing

Molecular-genetic testing is carried out for cases of NSCLC, while the adenocarcinoma cases include the detection of such mutations as *EGFR, ALK, ROS1, BRAF* as the obligatory minimal set along with the *KRAS* G12C (for which there are specific medications), *MET, RET, HER2* as an addition.

The results of genetical testing define the treatment tactics, the possibility of effective application of target therapy. At the same time, for the SCLC, the molecular-genetic testing is not routinely conducted, for in Russia there are no registered target therapy medications. The *DLL3* testing is not yet included into the routine practice in our country, but it is accessible within the frameworks of clinical research on target therapy (Ampuliximab).

Thus, the gold standard of differentiation between the SCLC and the NSCLC in the clinical settings is the IHC, but the development of new methods of diagnostics, especially the minimally invasive and non-invasive ones, is justified due to several key reasons:

1) in 15–20% of the patients, the biopsy is inaccessible due to the presence of concomitant diseases or due to the hardly accessible tumor location;
2) the invasiveness and the risks related to it (when conducting the bronchoscopy, there is a risk of pneumothorax and hemorrhages; transthoracic biopsy is especially dangerous in cases of central tumors or severe conditions);
3) high probability of false results due to the low quality of collecting the material and its fixation, as well as due to the heterogeneity of the tumor (biopsy can examine a limited area of the material and can miss the key mutations);
4) errors are possible that are caused by the complexity of interpretation (for example, large cell neuroendocrine cancer can mimic the SCLC);
5) the duration of testing procedures (sample preparation and IHC take up to 7–14 days, while in the regions with the deficit of histopathologists, the testing duration can be longer, which is critical for cases of aggressive SCLC);
6) IHC detects the subtype, but it does not replace the molecular test, as a consequence of which, the NSCLC requires further diagnostics using the method of polymerase chain reaction (PCR) / next generation sequencing (NGS).

All the problems described above create a strong need for developing the alternative approaches to differential diagnostics. A special interest is arising in the methods of fluid biopsy, such as the analysis of circulating tumor cells and of the extracellular DNA (ctDNA), the microRNA (miRNA), as well as the use of artificial intelligence in processing the radiography images.

PROMISING NON-INVASIVE ALTERNATIVES FOR THE DIFFERENTIAL DIAGNOSTICS OF NON-SMALL-CELL AND OF SMALL-CELL LUNG CANCER

Circulating tumor cells

The differentiation between the SCLC and the NSCLC using the circulating tumor cells (CTC) is based on the fact that SCLC shows a significantly higher concentration of CTC comparing to NSCLC, which allows for differentiating the tumor type [23]. The number of CTC correlates with the metastatic potential of the tumor, with the level of angiogenesis and with the prognosis for the patient [23–25]. Multiple research

works confirm that the number of CTC positively correlates with the poor prognosis [26, 27].

The isolation and the analysis of CTC for the primary diagnostic purpose opens the additional functional possibilities, such as creating the cell lines and testing the *in vitro* and *in vivo* treatment sensitivity, which can become an important step in personalized treatment. Special diagnostic interest arises from investigating the CTC clusters as an indicator of aggressiveness and of potential metastatic spreading. It is known that the presence of CTC clusters is indicative for high metastatic activity, especially in cases of SCLC [23].

The modern approaches for the detection of CTC include the following:

1) methods based on the EpCAM epithelial markers (epithelial cellular adhesion molecule) [28];
2) methods of negative selection (for example, CD45) [29];
3) microchip technologies (CTC-chip) [30];
4) size-dependent methods (ISET, ScreenCell, MCA) [31].

It is necessary to point out that the use of markers is characterized by low sensitivity, for it allows for detecting only the part of CTC population, missing the EpCAM-negative and the mesenchymal forms when using the EpCAM epithelial markers, as well as the CD45-negative cells when using the CD45-marker.

The key problems of CTC analysis for differential diagnostics are the insufficient standardization of methods and the biological heterogeneity of CTC. Significant complexity is added by the biological heterogeneity, when the differences between CTC-subpopulations (for example, by the degree of epitheliality /mesenchymality, by the presence of clusters) significantly complicate their precise identification, classification and developing the diagnostic and prognostic methods on their basis. Currently, the only system approved by the USA Food and Drug Administration (FDA) for the detection and quantitative determination of CTC in blood is still the CellSearch (CELLSEARCH®), while the majority of methods require further development and standardization [23]. The CellSearch system uses magnetic nanoparticles, covered in antibodies to the EpCAM epithelial marker for the detection of CTC, and the system is approved as the marker of predicting the survival rate in cases of metastatic breast cancer, prostate cancer and as a progression marker for metastatic colorectal cancer (CELLSEARCH®).

Thus, the use of CTC for the differentiation of SCLC and NSCLC represents a promising method, though still having a limited use in clinical practice. The most justified directions of development are deemed the combination of CTC analysis with testing the circulating extracellular tumor DNA and the implementation of the new uptake methods, based on the physical properties or negative selection, which could allow for taking into account the EpCAM-negative CTC subpopulations and for significantly expanding the diagnostic possibilities of this approach.

Circulating tumor DNA

DNA of the tumor cells, originating from the processes of apoptosis, necrosis and active secretion [24], enters the blood and other biological fluids, for example, the saliva, the sputum and others, potentially being the promising marker for non-invasive diagnostics of oncological diseases. Multiple research works have revealed the principal differences in the mutation profiles of SCLC and NSCLC. Thus, the SCLC is characteristic by the inactivation of the *TP53* and *RB1* suppressor genes [15, 21], as well as the mutually exclusive expression of *MYCL*, *MYC* or *MYCN* [15, 32–35]. These changes are considered the most important for the development of small-cell phenotype and the ones that are closely related to its neuroendocrine nature. NSCLC, unlike the SCLC, demonstrates a more variable spectrum of genetic changes, significantly differing between the histological subtypes. Lung adenocarcinomas — the most widespread NSCLC variants — often carry the activating mutations within the *EGFR* and *KRAS* genes, as well as the rearrangements in the *ALK* and *ROS1* genes [17–20]. Squamous carcinoma, on the contrary, rarely has these changes, but often contains amplifications in the *SOX2, PDGFRA, FGFR1/WHSC1L1* genes along with the deletions of *CDKN2A* [36, 37] and the mutations of *PIK3CA* [38]. Modern methods of molecular diagnostics, such as NGS and PCR, allow for highly precise detecting these differences. NGS-panels provide the possibility of combined evaluation of the mutation status, while PCR has an exclusive sensitivity for the detection of specific mutations, such as the *EGFR* and others. As an example of the NGS-panel, one can take MSK-IMPACT — the first FDA-approved combined genomic test for onco-diagnostics, developed at the Memorial Sloan Kettering Cancer Center in the USA, which analyses more than 400 cancer-associated genes and which is being used in clinical practice predominantly for

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the diagnostics and personalized treatment of solid tumors, including the NSCLC [39]. In Russia, there are already registered NGS-panels for the diagnostics of LC, for example, the ones manufactured by the companies “OnkoAtlas” and “Helikon”.

Not less important are the differences in the copy number variations (CNV) between SCLC and NSCLC. The small-cell cancer is characteristic by the amplification of the oncogenes *MYC* (20% of the cases [40]) and *SOX2* (27% [35]), as well as frequent deletions in the 3p chromosome region, involving the *FHIT* gene [41]. These changes are associated with especially aggressive disease course. With this, the increased expression of *SOX2* was also found in cases of SCLC, while in the NSCLC (adenocarcinoma and squamous LC), as it appears, the specific marker functions of *SOX2* are still to be determined. Nevertheless, even now, a high potential was defined for using *SOX2* as the target for therapeutic procedures [42]. The NSCLC, on the contrary, often has amplifications of *EGFR* and *MET* — 5–15% (in case of adenocarcinoma [43, 44]) or *CCND1* (in squamous-cell cancer [45]), as well as the deletions of *CDKN2A* [46]. The CNV analysis allows for not only differentiating the subtypes of LC, but also to isolate the prognostically unfavorable variants, such as the SCLC with *MYC* amplification [40]. Modern approaches combining the analysis of the mutation profile and the copy number variations, significantly increase the precision of diagnostics (by 27%), while using the methods of fluid biopsy is topical for the diagnostics of SCLC [47]. These data, as well as the methods of their collection and analysis, are already used in the development of modern clinical recommendations in America and Europe, including the NCCN and ESMO guidelines.

The assessment of abberrant methylation of the circulating DNA

DNA methylation is an epigenetic modification, in which the cytosine in the CpG-dinucleotides gets a methyl group added. This modification influences the expression of genes by suppressing the transcription: the methylation of promotor regions blocks the binding of transcriptional factors and attracts the proteins, compacting the chromatin, which “switches off” the gene. In the pathogenesis of LC, methylation abnormalities manifest as the two opposite processes. On the one hand, there occurs the global hypomethylation, activating the mobile genetic elements and the oncogenes, which promotes to the genomic instability. On the other hand, hypermethylation of promotor regions of the suppressor genes of tumor growth, such as *p16INK4a* and *BRCA1*, lead to their functional inactivation and to the acceleration of tumor cell proliferation.

As of today, there is a large number of methods for analyzing the methylation status of specifically the extracellular DNA [48], while the modern research works clearly demonstrate their diagnostic value. It was found that various histological subtypes of LC are characterized by the unique methylation patterns of the circulating free DNA (cell-free DNA, cfDNA): for example, the analysis of the *APC, HOXA9, RARβ2* and *RASSF1A* genes can define the types of LC and the stage of the disease [49]. Moreover, the classifiers based on the analysis of the cfDNA methylation, investigated in various research works, have allowed for isolating not only the types of LC between each other [50], but also the subtypes of SCLC [51, 52] and NSCLC [50, 53]. However, the high specificity of analyzing the methylation of separate markers (often >80%) in these research works is accompanied by low sensitivity (~50–65%). The decision for this problem could be the expansion of the panels for the simultaneous analysis of methylation among the several markers.

Beside the use for the diagnostic purposes, the analysis of methylation profile could also be informative for the evaluation of treatment tolerance [52]. A separate problem when developing various diagnostic methods is the risk of false-positive results due to the presence of background methylation, especially in smokers [54], which is critically important in case of LC and requires additional research.

The proof of the efficiency of using the methylated markers for fluid biopsy in LC is the presence in the European and Chinese markets of several diagnostic tests aimed at the diagnostics of LC (CE-IVD mark [55]) and approved by the Chinese National Medical Products Administration (NMPA) [56] and by the American FDA [57].

Thus, the analysis of cfDNA methylation represents a promising tool for the non-invasive and specific diagnostics of SCLC and NSCLC, nevertheless, further development is needed in the field of compiling the panels for the evaluation of multi-gene methylation and for the automated analytical platforms, which requires arranging additional validation studies.

Aberrant expression of microRNA

MicroRNA are considered the promising biomarkers for the differential onco-diagnostics due to their

stability in biological fluids and tissues, as well as due to the ability to reflect the molecular specific features of the tumor. Multiple research works demonstrate that the microRNA expression profiles both in blood plasma and in blood exosomes significantly differ in cases of NSCLC and SCLC, which opens new possibilities for developing the non-invasive diagnostic tests [58, 59]. Indeed, microRNA can be found in blood both at the free state and as a part of membrane-coated micro-vesicules [60–64]. The significant part of blood micro-vesicules is represented by exosomes — the vesicules with a diameter of 30–150 nm, which get released by the normal and by the tumor cells and take part in the intercellular communication. Exosomes/micro-vesicules of tumor origin contain proteins, nucleic acids and lipids reflecting the molecular profile of the tumor. Blood micro-vesicules are evidently a more acceptable source of microRNA for diagnostic purposes than blood plasma: data from a number of research works provide strong evidence of the greater enrichment of this microRNA pool with tumor-specific microRNA [65].

The majority of studies is devoted to evaluating the expression of microRNA in NSCLC and its subtypes, while the SCLC, due to its lesser incidence has gained insufficient attention. A comprehensive research on the microRNA-31 expression using the method of quantitative polymerase chain reaction with reverse transcription (RT-PCR) in lung tissue samples obtained after surgical resection in cell lines and in tumor xenotransplants from mice, along with the available data from the Cancer Genome Atlas (TCGA) has shown that microRNA-31 is variously expressed in the tumors of various histological types of LC. In particular, excessive microRNA-31 expression was found in the NSCLC samples (lung adenocarcinoma, squamous carcinoma, adeno-squamous carcinoma and large cell neuroendocrine carcinoma), however, the samples of small-cell carcinoma and atypical carcinoids did not show any increase of the expression [66], which allows for suggesting the high potential of using microRNA-31 as the molecular marker of NSCLC.

In another research, the evaluation of the microRNA expression profiles in the SCLC and NSCLC cell lines along with the normal immortalized human bronchial epithelium cells using the microchips test has revealed a number of differentially expressed microRNA. In total, 29 microRNA were statistically significantly differentially expressed in the SCLC and NSCLC cell lines, of which 19 (-15a,b, 16, 195, 135, 106a,b, 101, 338, 1, 98, 103, 107, 17-5p, 92, 93, 326, 328, 96) were hyper-expressed in the SCLC cell lines comparing to the NSCLC, and 10 (-21, 22, 23a,b, 24, 27a, 29a,b,c, 31) — had a decreased expression [67]. Significantly differing microRNA expression in SCLC comparing to NSCLC and to the normal immortalized human bronchial epithelium cells allows for suggesting that the microRNA expression profiles can be successfully used for the differential diagnostics of these LC variants.

Another research has developed and validated a panel of eight microRNA (106a, 125a-5p, 129-3p, 205, 21, 29b, 375, 7) using the pathological and the cytological LC samples. It was found that this panel, named as the “miRview lung”, can be used for the differentiation of SCLC and NSCLC (in particular, the squamous and the non-squamous lung carcinoma or carcinoid). The research work was arranged in three stages: detection stage, at which the potential biomarkers were identified; the test development stage, during which the marker microRNA were selected and the classifier was compiled; and the validation stage, at which the diagnostic protocol was tested using the blinded independent sample. The total precision of the analysis was 93.7% (95% CI 90.8–95.8) [68]. Despite the optimistic results, the research did not result in the appearance of the LC diagnostic system on the market, which seems to be related to the specific features of the analytical system or to the group of donors and patients involved into the research.

NSCLC is the most widespread type of LC, being responsible for up to 85% of all the cases. For this reason, multiple research works were arranged for the identification of microRNA, which can differentiate the histological subtypes of NSCLC, in particular, the lung adenocarcinoma and the squamous LC. For example, in the research based on the analysis of blood microRNA in 90 LC patients and in 85 healthy volunteers, microRNA-944 has shown the diagnostic efficiency for operative detection of squamous LC (area under the curve, AUC, 0.982), while the microRNA-3662 was effective for detecting the operable lung adenocarcinoma (AUC 0.926) [69]. In another research of microRNA expression in blood plasma, a panel was compiled for the diagnostics of lung adenocarcinoma, consisting of seven circulating microRNA (9-3p, 96-5p, 147b-3p, 196a-5p, 708-3p, 708-5p, 4652-5p), as well as the panel for the diagnostics of squamous LC, containing nine various microRNA (130b-3p, 269-3p, 301a-5p, 301b-5p, 744-3p, 760, 767-5p, 4652-5p, 6499-3p) [70].

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Summarizing the abovementioned, modern research works demonstrate the significant potential of microRNA as the specific biomarkers for the differential diagnostics of LC subtypes. As shown by the data, the unique microRNA expression profiles in the tissues, blood plasma and exosomes allow for clearly differentiating the NSCLC and the SCLC with an accuracy of up to 93.7% [68]. Special attention deserve the microRNA panels effectively differentiating the SCLC from the NSCLC, and the developments based on the analysis of the circulating microRNA, opening the possibilities for the non-invasive diagnostics [69]. For the standardization of the panels and their implementation into the Clinical laboratories, further multi-center research works are necessary with the unified protocols of the isolation, the analysis of microRNA and the normalization of the obtained data. Nevertheless, already as of today, microRNA represent a powerful tool in personalized oncology, capable of improving the precision of diagnostics and the treatment tactics for the LC patients.

Protein markers

Modern research works differentiate several classes of candidate proteins, demonstrating the differential expression in cases of SCLC and NSCLC. These include the neuroendocrine differentiation proteins (ProGRP, NSE), the cytokeratins and their fragments (CYFRA 21-1), the adhesive molecules (EpCAM, CEACAM), the embryonic antigens (CEA), the carbohydrate antigens (CA 125, CA 19-9). High level of neuroendocrine differentiation proteins is observed in cases of SCLC, while the other protein markers are elevated in cases of NSCLC. Thus, the levels of ProGRP (pro-gastrin-releasing peptide) — one of the most SCLC-specific markers, related to the neuroendocrine origin of the tumor — in the blood serum clearly correlate with the histological type of LC: abnormal levels of ProGRP are detected in 60–70% of the patients with localized stage of SCLC and in 75–90% of the patients with the advanced stage of the disease, while the elevation of ProGRP level to 120 pg/ml was observed only in 4% of the NSCLC cases. As for the adjacent areas of application, according to the data from the multifactorial analysis, ProGRP has no independent prognostic value [71]. Another protein — NSE (neuron-specific enolase) — acts as the highly specific marker for the neurons and peripheral neuroendocrine cells. Taking into consideration the location of NSE in certain tissues at the normal state, the elevation of its level in biological fluids can indicate the presence of malignant proliferation and have a diagnostic value for the detection, the staging and the treatment of neuroendocrine tumors. NSE is more often increased in cases of SCLC, however, its specificity is lower comparing to the ProGRP, due to the possible elevation in a number of other diseases (for example, in cases of neuroblastoma, melanoma, seminoma etc.) [72].

The levels of serum biomarkers, such as the serum amyloid A (SAA) and CYFRA 21-1, are increased in cases of NSCLC, especially in squamous-cell cancer and adenocarcinoma, which allows for using them for the differentiation with SCLC [73]. Carcinoembryonic antigen CEA and the CEACAM carcinoembryonic antigen-related cell adhesion molecule are more often associated with adenocarcinoma and other forms of NSCLC, but can be also elevated in cases of SCLC, which decreases their specificity. In the detailed review of the available literature data, it was shown that serum CEA has an independent prognostic and predictive value in cases of NSCLC regardless of the type of treatment, however, its diagnostic value is insignificant [74]. SCC (squamous-cell carcinoma antigen) — the marker of squamous carcinoma, one of the subtypes of NSCLC, is useful for the differentiation of SCLC. The CA 125, CA 19-9 and CA 15-3 markers are being investigated in a context of NSCLC, especially the adenocarcinoma. It was shown that the levels of CEA, SCC, CA 125, CA 15-3 and TAG-72-3 were significantly higher in NSCLC cases as compared to the SCLC [75].

A number of research works have shown that various combinations of markers, for example, ProGRP and NSE, CYFRA21-1 and SCC-Ag, or CEA + CYFRA 21-1 + SCC/CA 15.3, allow for considerably increasing the sensitivity and specificity parameters comparing to the single marker protein [74–77]. Special diagnostic interest arises from the fact that many of these markers not only reflect the histogenetic features of the tumor, but also correlate with the activity of specific molecular pathways, which opens the potential possibilities for using them in personalized therapeutic strategies.

Thus, the special interest for the differential diagnostics is gained specifically by the proteins associated with the neuroendocrine differentiation (ProGRP, NSE) for the SCLC and with the epithelial tumors (CYFRA 21-1, CEA etc.) for NSCLC. Their detection in blood serum bears a significant diagnostic potential, allowing for not only differentiating the cancer subtypes, but also for evaluating the dynamic changes of the disease during the treatment course. However, none of the known markers shows the

absolute specificity, which dictates the necessity of searching the optimal combinations and developing the standardized algorithms of interpretation.

Exosomal proteins

Low concentrations of tumor-specific proteins in blood plasma/serum oftentimes do not allow to reliably detect these proteins using the accessible methods, with this, the exosomes secreted by the tumor cells (and other micro-vesicules) can be concentrated and "washed off" from the ballast blood plasma proteins, or the proteins produced during the blood cell lysis, which will significantly simplify their further analysis. Indeed, it was shown that exosomal proteins can be used for the diagnostics of oncological diseases: for example, the exosomal markers CD151, CD171 and tetraspanin 8 have a significant potential for the diagnostics of oncological diseases in the lungs in general [78]. As for the differential diagnostics of LC types, encouraging results were obtained: for example, integrin αV is expressed in the exosomes of cancer cells of both LC types, while the epithelial-specific heterodimer of integrin α6β4 was selectively expressed in the exosomes of NSCLC [79]. At the same time, there is only a small number of comparative research works on the exosomes in NSCLC and SCLC patients. In particular, it was found that the expression of JUNB and CXCR4 is increased in the exosomes of SCLC patients comparing to the healthy donors, however, it remained unclear if there are differences in the expression levels of these proteins in the exosomes of NSCLC patients [80]. The most part of research works is devoted to studying the most widespread NSCLC. Thus, M. Bao et al. [81] have found the exosomal proteins having the potential for the diagnostics, the staging and the prognosis of this disease.

It is necessary to note that there is a number of problems limiting the use of exosomes for the diagnostics of oncological diseases, including the LC. First of all, the applied methods of extraction and analysis of the exosomal proteins are heterogenous and require unification. Secondly, the exosomes present in the biological fluids have various origin, including the non-tumor one. Such exosomes have a set of markers typical for healthy cells, which can complicate the identification of marker proteins. Thirdly, the majority of models were built using the small and limited samples, while it is necessary to arrange the large prospective research, solving the validation objective. Thus, the exosomal proteins demonstrate strong potential for the differential diagnostics, for the predicting and the monitoring of SCLC and NSCLC, however, the evaluation of their clinical value requires the development of standardized protocols, large-scale multi-center research and, probably, the inclusion of proteomic data into the multiomic diagnostic systems.

Radiomics

Radiomics — the extraction and analysis of data obtained from the medical images — is a rapidly developing modern field of Medicine. The development of the reliable systems for computed diagnostics using artificial intelligence is already acknowledged as important by the part of research works in medical visualization. The algorithms based on artificial intelligence are learning to process the visualization data with further setting the diagnosis. There is a whole number of research works demonstrating the possibilities of artificial intelligence in the diagnostics, the staging, in predicting and sub-typing the NSCLC [82–85]. In general, the majority of models demonstrate the diagnostic efficiency that is comparable or even exceeding the efficiency of the experts, while the general problems are the reproducibility and the adaptation for use in clinics [82]. At the same time, despite the active usage of the artificial intelligence approaches for sub-typing the NSCLC, very few research works are aimed at solving the tasks of differential diagnostics of SCLC and NSCLC using CT/PET data [86-89]. The specific features of the clinical course of SCLC (higher mortality) and the diagnostics routing often result in the lesser extent of visualization data (especially PET/CT), applicable for radiomic analysis, which, in turn, explains the significant sub-representativity of clinically and morphologically confirmed cases of SCLC in the public and institutional PET/CT visualization data sets. For example, the data set (the structurized collection of data) from the TCIA (Cancer Imaging Archive) for non-small-cell lung cancer (NSCLC) of the Radiogenomics dataset (cancerimagingarchive.net) (https://www.cancerimagingarchive.net/collection/nsclc-radiogenomics/), compiled in 2018, includes only the cases of non-small-cell cancer, and the widely used LIDC-IDRI, compiled by the Lung Image Database Consortium and by the Image Database Resource Initiative (cancerimagingarchive.net) (https://www.cancerimagingarchive.net/collection/lidc-idri/) contains no histological verification. Thus, there is an urgent need for creating the SCLC specialized data sets.

Nevertheless, several commercial platforms are already available for solving the similar tasks by means of radiomics: they include the OncoRadiomics

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(OncoRadiomics SA — the compilation of the prognostic model for NSCLC), the IBEX (IBM Watson Health — research on NSCLC), Mirada Medical (Canon Medical Systems — building the validated models for predicting the response to immunotherapy; HealthMyne — compiling the prognostic models for SCLC).

Thus, the statistically insignificant share of SCLC cases in the data sets and the insufficient standardization of visualization protocols significantly restrict the possibilities of developing and validating the artificial intelligence models, directed at the non-invasive differential diagnostics of SCLC and NSCLC, nevertheless, separate research works devoted to this problem [85–88] and the advance in the adjacent fields indicate that radiomics based on machine learning can be used for the differentiation of SCLC from the NSCLC along with other lung neoplasms, it also can be included into the multimodal diagnostic systems (for example, including the CT, the PET, the clinical data and the molecular markers).

Volatile organic compounds

Volatile organic compounds (VOC) represent the low molecular mass (<300 Da) metabolites, excreted by tumor cells as a result of abnormal metabolism. These compounds (alkanes, ketones, aldehydes, aromatic carbohydrates) enter the circulation and become excreted via the respiratory system, which makes them the promising non-invasive biomarkers [90]. The biological significance of VOC comes from their direct relation to the key oncological processes. This field is being actively developed, for it allows for detecting the molecular patterns reflecting the differences in the metabolism of various types of tumor cells. The method of gas chromatography–mass-spectrometry (combining the gas chromatography and mass spectrometry — GC-MS) is the gold standard in detecting the LOC, that allows to precisely identify the individual volatile compounds.

Non-invasive tests based on detecting the VOC are also being developed for the differential diagnostics of SCLC and NSCLC [91]. Specific metabolites were identified that differentiate the VOC-profiles of SCLC from the NSCLC. Some compounds, such as alkanes, show the presence of high correlation with LC, which indicates the high practicability of using the specific VOC for its diagnostics [92]. As for the differential analysis of SCLC and NSCLC, controversial results were obtained here. Thus, in the research involving the number of cell lines, the analysis of VOC and metabolites has allowed for significantly differentiating the LC and the normal cells, as well as the SCLC and the NSCLC, including various NSCLC subtypes. SCLC differed from NSCLC by m- and p-xylenes, ethyl-benzol, styrene, o-xylene, 1.3-bis(1.1-dimethylethyl)-benzol and 2.4-bis(1.1-dimethylethyl)-phenol, and each of these VOC had an AUC value above 0.95 [93]. Another research has analyzed VOC in patients with NSCLC and SCLC along with healthy donors, and, though it successfully helped differentiating the patients and the healthy donors, it was not successful in the differentiation of LC subtypes [94]. The analysis including the research on the differences of VOC profiles between the SCLC and the NSCLC, has revealed an elevation of hexanal levels (p <0.006) in cases of SCLC [95], however, the observed differences were presumably related to higher malignancy and increased tumor cell activity in the SCLC. Thus, the issue on how effectively it is possible to differentiate SCLC and NSCLC based on the VOC, remains unsolved and requires further research.

The promising approach to analyzing the VOC are the artificial sensory systems, or the “electronic nose” (eNose). eNose is the integrated system, mimicking the olfaction with the main task being the recognition and classification of complex VOC-mixtures; it includes a sensor module and the data processing system (algorithms of machine learning, the method of main component, the linear discriminant analysis etc.), which classifies the tested “odor”. The sensor module can use various technologies: gas chromatography, gas sensors based on semiconductors with metal oxide (metal-oxide-semiconductor, MOS), devices with combined sensors made of conducting polymers, quartz microbalance (QMB), the colorimetric sensors, the chemical resistors and the superficial acoustic waves [96]. “Electronic noses”, generally, do not identify specific compounds, but operate with a combined odor “fingerprint”. The artificial sensory systems quickly analyze the VOC-profiles of the expiratory air and use the machine learning algorithms for classifying the type of tumor. Currently there is a limited number of research works evaluating the efficiency of such an odor “fingerprint” for the diagnostics of SCLC and NSCLC patients, with this, encouraging results were obtained that show the sensitivity/specificity of the differential diagnostics of SCLC and NSCLC when using the eNose equaling 87% [97]. Despite the optimistic findings in this field, there is still a number of problems to solve, among which, for example, is the effect of unspecified factors on the precision of detecting the LOC, the contribution of individual

specific features of the patients into the specificity of diagnostics (for example, VOC characteristic for LC, can be also excreted in cases of chronic bronchitis or chronic obstructive pulmonary disease) [98]. Besides, an important contribution to the concentration of VOC is made by the individual variations, for the metabolism of VOC depends on the age, the gender, the diet, the smoking and the microbiome of the oral cavity [99, 100]. VOC analysis based on the eNose is a promising tool for the non-invasive differentiation of SCLC and NSCLC, especially for developing the screening tests, for it allows for conducting a rapid and non-invasive testing, however, its sensitivity and specificity require large-scale and profound research.

CONCLUSION

The modern differential diagnostics of SCLC and NSCLC is experiencing a period of active transformation, transitioning from the traditional invasive methods to the combined non-invasive approaches. Despite the undisputed significance of the immunohistochemical examination as the golden standard, its limitations stimulate the development of principally new diagnostic strategies.

The promising directions including the analysis of circulating tumor cells, of the extracellular DNA, of the exosomal markers, the microRNA and the volatile organic compounds, demonstrate the significant diagnostic potential. Parallel development is observed in the methods of radiomics and artificial intelligence, opening new possibilities in processing the medical images and multiomic data. However, the transition of these technologies into clinical practice meets a number of methodological and practical difficulties. The key issues remaining are the standardization, the reproducibility and the validation of new methods. With this, the differential diagnostics of rare and aggressive forms of cancer, such as the SCLC, represents a special complexity.

The future of differential onco-diagnostics, undoubtedly, belongs to the multimodal methods, integrating the advances in the fluid biopsy, the radiomics and the artificial intelligence into the unified diagnostic algorithms. It is specifically the synergy of various diagnostic approaches that will allow for overcoming the limitations of separate methods and for achieving the new level of precision. And, in achieving it, the important role in the processing of multimeric data, will be played by the modern algorithms, including the method of the main components, the linear discriminant analysis, the random forest method, the reference vectors method and the neuron networks (including the deep learning). The combined approach to the diagnostics of lung cancer with taking into consideration the individual characteristics of the patient will also open new possibilities for the personalized treatment, which ultimately will significantly improve the quality and the duration of the patients' life.

ADDITIONAL INFORMATION

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Comorbidity Background and Rehabilitation Potential Among the Cerebral Stroke Patients

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ABSTRACT

Stroke is one of the most significant social problems due to the high incapacitation rates among the patients. The rehabilitation of the patients in the older age group with stroke consequences is complicated by the fact that they almost always have a comorbidity background, influencing the efficiency of restoring the lost functions and the possibilities of using any technologies of medical rehabilitation. Comorbidity makes its contribution to the development of repeated stroke and plays a significant role when drafting the rehabilitation program. The review analyzes the data from scientific literature on the effects of concomitant diseases on the rehabilitation potential of patients after a past acute cerebrovascular accident. An analysis was carried out for the literature data using three data bases (PubMed, MEDLINE and eLIBRARY) for the period from 2000 until 2025 with 435 scientific articles analyzed, and for the detailed analysis, 35 publications were selected that meet the inclusion criteria. Based on the analysis conducted, various options were presented for evaluating the rehabilitation potential and for interpreting the evaluation results with taking into consideration the effect of various diseases, most frequently seen in patients with acute cerebrovascular accident. A discussion is presented on the necessity of compiling a single unified method of determining the rehabilitation potential. The analysis of literature data has shown that evaluating the comorbidity is one of the important components of the rehabilitation potential in the patient after the stroke. Determining the most significant factors shaping the rehabilitation potential in such patients is a top priority task determining the choice of rehabilitation therapy tactics and its efficiency.

Keywords: *rehabilitation potential; concomitant diseases; comorbidity; medical rehabilitation; stroke; incapacitation.*

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INTRODUCTION

Stroke is the leading disease in terms of the degree of incapacitation among the patients. According to statistical data, among the surviving patients, to the end of acute period of the disease, more than 80% have persisting motor and cognitive disorders of various degree of intensity [1]. For achieving the maximum treatment effect, the medication therapy must be obligatorily combined with medical rehabilitation and with preventive measures [2].

Medical rehabilitation is an integral part of treating the patients after an acute cerebrovascular accident (CVA) and it must be used taking into consideration the mechanisms of spontaneous convalescence in the acute, the subacute and the recovery periods of stroke, as well as during the period of residual effects [3]. With this, one of the important problems remaining is the risk of repeated stroke, which is approximately 30% and which is most frequently developing in the first two years after the CVA [4], which has great importance for organizing the rehabilitation and preventive activities. The World Health Organization has verified more than 300 various risk factors of developing the CVA, however, the top priority ones are only the factors which show a high rate of incidence in various populations, significantly affecting development of stroke, and influencing which by means of timely preventive activities decreases the CVA incidence. The combination of several such factors increases the risk of developing the CVA [5]. The age plays a significant role in determining the program of rehabilitation activities, for the elderly patients in the majority of cases have a comorbidity background influencing the rate of reparative processes and the possibility of using various technologies of medical rehabilitation [6]. Thus, investigating the role of concomitant diseases in stroke patients at all the stages

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Коморбидный фон и реабилитационный потенциал пациентов после перенесённого церебрального инсульта

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АННОТАЦИЯ

Инсульт является одной из наиболее значимых социальных проблем вследствие высокого уровня инвалидизации пациентов. Реабилитация пациентов старшей возрастной группы с последствиями инсульта затрудняется тем, что у них почти всегда присутствует коморбидный фон, оказывающий влияние на эффективность восстановления утраченных функций и возможность применения тех или иных технологий медицинской реабилитации. Коморбидность вносит свой вклад в развитие повторного инсульта и играет значимую роль при составлении программы реабилитации. В обзоре проанализированы данные научной литературы о влиянии сопутствующих заболеваний на реабилитационный потенциал пациентов после перенесённого острого нарушения мозгового кровообращения. Проведён анализ литературы по трём базам данных (PubMed, MEDLINE и eLIBRARY) за период с 2000 по 2025 год, проанализированы 435 научных статей, для детального анализа отобрано 35 публикаций, соответствующих критериям включения. На основании проведённого анализа представлены различные варианты оценки реабилитационного потенциала и интерпретации результатов оценки с учётом влияния различных заболеваний, наиболее часто встречающихся у пациентов с острым нарушением мозгового кровообращения. Анализ литературы показал, что оценка коморбидности является одной из важных составляющих реабилитационного потенциала пациента после перенесённого инсульта. Определение наиболее значимых факторов, формирующих реабилитационный потенциал у таких пациентов, является первостепенной задачей, определяющей выбор тактики реабилитационного лечения и его эффективность.

Ключевые слова: *реабилитационный потенциал; сопутствующие заболевания; коморбидность; медицинская реабилитация; инсульт; инвалидизация.*

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of treating the disease must become the obligatory component of modern neuro-rehabilitation.

The problem of the unified evaluation of the rehabilitation potential is primarily resulting from the needs of the physicians in having the instrument allowing for timely getting an insight on the potential of restoring various abnormalities of the vital processes with a certain comorbidity background. Besides the medical aspect, this problem has the regulatory and the economical ones.

Regulatory requirements. A Decree issued by the Ministry of Health with a number 788n[1] regulates the obligatory determination of the rehabilitation potential in the patients at all the stages of medical rehabilitation, beginning from Day 1 of disease development and of admittance to the in-patient department. The clinical recommendations on medical rehabilitation for various diseases and conditions of the nervous system also regulate the determination of the rehabilitation potential during the process of providing the aid on medical rehabilitation from the first stage of medical rehabilitation of the patients in the peracute and the acute periods of ischemic stroke, beginning from the Department of Anesthesiology and Resuscitation.

Economical aspect. The possibility of timely and objectively defining the rehabilitation potential determines not only the further adequate routing of the patient, but also the extent of costs for using

[1] Decree issued by the Ministry of Healthcare of the Russian Federation on July 31, 2020, No. 788n “On the Approval of the Procedure for the Organization of Medical Rehabilitation of Adults” (registered on 25.09.2020, No. 60039). Access mode: http://publication.pravo.gov.ru/Document/View/0001202009250036

the medical services and the medical rehabilitation technologies, applicable for the treatment of a specific patient. In the evaluation of the economical component of the rehabilitation in patients with a past cerebrovascular stroke, separate attention should be paid to the personnel aspect — the efficiency of using the staff potential of the medical organization involved into the rehabilitation. For the reason that the staff resources of the rehabilitation service is always the limiting factor, the involvement of specialists from the multidisciplinary rehabilitation team (medical logopaedist, neuropsychologist, medical psychologist, ergo-rehabilitation specialist, physical rehabilitation specialist etc.) in everyday practice should be maximally rational and should be conducted primarily for the patients with high and medium rehabilitation potential.

Search methodology

An analysis was carried out using the full-text publications in Russian and English languages from the PubMed, MEDLINE and eLIBRARY data bases for the period from 2000 until 2025 using the following key words: “rehabilitation potential in stroke”, “prognosis after a stroke”, “stroke outcome”; as the second search criterion, the queries used were “concomitant disorders”, “comorbidity” and “concomitant diseases”. During the initial search, 435 sources were extracted, of which 35 research works were selected as meeting the inclusion criteria (comorbidity was analyzed at least by one specific rehabilitation result, including the functional status).

THE MAIN COMORBID FACTORS DEFINING THE REHABILITATION POTENTIAL

Due to the fact that rehabilitation potential is an integrative parameter, requiring the multimodal approach to evaluating various factors of the patient’s activity, the special role belongs to the evaluation of the presence and the severity of the concomitant diseases present, which may directly affect the potential of restoring the impaired or decreased functions, as well as the adaptation in cases of lost functions.

According to the literature data, patients with cerebrovascular diseases are most commonly prone to developing the circulatory diseases, which, in turn, not only increases the risk of cerebral accident, but also prognostically negatively affects the outcome and the level of incapacitation [7]. Hypertensive disease and heart rhythm disorder, namely the atrial fibrillation, have a certain role not only in the development of stroke, but they also affect the potential of restoring the lost functions. Atrial fibrillation is the reason of developing vast infarctions and, as a result, it leads to a decrease in the rehabilitation potential and to more severe functional outcomes [8]. The presence of atrial fibrillation in the ischemic stroke patients is not only the predictor of developing more extensive lesions in the brain, but also the factor increasing the mortality rates [9–12]. Arterial hypertension, with its specific changes in the vascular wall, with the specific features of systemic or cerebral circulation and metabolic disorders, is also one of the main reasons of developing the CVA [13]. Patients suffering from hypertensive disease, according to the definition from the World Health Organization, already are at very high risk of cardio-vascular complications, which requires special attention to the adequate and timely prescribing of medication therapy [14]. With this, a number of research works reports that the percentages of patients suffering from arterial hypertension and having a past episode of the initial and repeated CVA, are approximately equal [15].

The elderly age and the presence of cardiac comorbidity are the factors of significant influence on the rehabilitation potential and the functional outcome of rehabilitation after the cerebral stroke [8, 16]. The results from a number of publications show that the presence of chronic cardiac failure itself is a factor restricting the rehabilitation potential and also is an independent risk factor for mortality during various periods of the disease [17, 18]. This effect is associated not only with the limited extent and the technologies applicable during the process of medical rehabilitation, but it is also a limitation of the functional reserves in the organism, which makes it impossible to use a number of technologies and methods of medical rehabilitation in the given category of patients. The presence of cardio-vascular diseases itself is a factor limiting the arrangement of medical rehabilitation, while in the neglected cases — a risk factor for the medical rehabilitation itself [19].

METHODS OF EVALUATING THE REHABILITATION POTENTIAL

Initially, for the purpose of defining the rehabilitation potential, a CIRS system (Cumulative Illness Rating Scale) was proposed [20]. Later on, taking into consideration the specific features of the cerebral stroke patients, the preference was given to the modified version of this score — the CIRS-G (Cumulative Illness Rating Scale-Geriatrics), evaluating the specific features of the patients from the older age group, the one that is most prone to developing the CVA [21]. This scale is quite

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comfortable to use and it has a high number of electronic assistants, beginning from online-applications and moving on to online-calculators with the detailed hints for the specialists on its correct filling. The backbone of this score is the evaluation of the presence/severity of impairments in each of the system of organs, the need for therapy to correct the available diseases. The result of questionnaire survey is the interpretation of the severity of the concomitant diseases present [21] (table 1). Along with the CIRS-G score, the proposed options included the use of the Charlson Comorbidity Index (CCI) for scoring the presence or the absence of the certain diseases, applicable for predicting the mortality [22] (table 2). The comparison of the Charlson index and the CIRS-G comorbidity score has shown higher validity of the latter in the evaluation of the parameters in all the categories of patients, with this, the evaluation of the rehabilitation potential was carried out using the classification proposed by A.R. Sagatov, in which the rehabilitation potential is graded as high, medium, low and absent [23].

Most commonly, the evaluation of the rehabilitation result after a cerebrovascular stroke employs a Functional Independence Measure (FIM). Some research works have studied the effects of concomitant diseases on the dynamic changes of the cognitive functions, evaluated using the combination of validated clinical scales — the Mini-Mental State Examination (MMSE), the Hospital Anxiety and Depression Scale (HADS), the Montreal Cognitive Assessment (MoCA) and the Barthel Activities of Daily Living [ADL] Index [9, 24–37] (table 3). Out of the 13 publications using the FIM, 10 were employing the total comorbidity index, while other 3 were focused on the specific concomitant diseases. Three retrospective research works were employing the Charlson index for the evaluation of

Table 1

The table for calculating the significant comorbidities in the patient — CIRS-G (Cumulative Illness Rating Scale-Geriatrics)

Organs and systems	Points	Interpretation
Heart	0	Vessels Level 0: no problems. Level 1: hypertension, compensated by restriction of cooking salt and by decreasing the weight / serum cholesterol >200 mg/dl. Level 2: daily intake of anti-hypertensive drugs / single atherosclerosis symptom (claudication, vascular murmurs, transient vision loss, absence of pulse in the feet) / aortic aneurism <4 cm. Level 3: two or more atherosclerosis symptoms (see below). Level 4: surgical interventions due to vascular problems / aortic aneurism >4 cm. *Comments.* The arterial hypertension is defined as stable increase of diastolic pressure >90 mm.Hg. Absence of necessity for medication therapy — “1”; single daily intake of a drug for decreasing the BP — “2”; daily intake of two or more drugs for the control of BP or the presence of signs of hypertrophy in the left ventricle — “3”. Atherosclerosis of peripheral vessels. Presence of at least one symptom upon physical examination or confirmation by the imaging methods (for example, angiography) — “2”; the presence of two or more symptoms — “3”; if by-passing was done or required — “4”. The impaired cerebral circulation is evaluated in the nervous system section. Aneurism of the aorta: diameter <4 cm — “3”; >4 cm — “4”
Vessels	0	
Hematopoietic system (blood, vessels, bone marrow, spleen, lymphatic system)	0	
Respiratory system (lungs, bronchi, trachea from the laryngeal level)	0	
ENT-organs	0	
Upper GIT (esophagus, stomach, duodenum)	0	
Lower GIT (intestine, herniations)	0	
Liver (including bile ducts and pancreatic ducts)	0	
Kidneys	0	
Urogenital system (urinary ducts, urinary bladder, urethra, prostate gland, genitals, uterus, ovaries)	0	
Locomotor system, skin and mucosal membranes	0	
Nervous system	0	
Endocrine system / metabolic disorders and mammary glands (including infection and poisonings	0	
Psychiatric diseases	0	
Assessment of malignant tumors	0	
Other diseases	0	

Note. The calculation table estimates the geriatric variant of the cumulative comorbidity index CIRS-G according to guideline by M.D. Miller et al., 1991 [21]. GIT — gastrointestinal tract; BP — blood pressure.

Table 2

Charlson Comorbidity Index

Points	Diseases
1	Myocardial infarction Congestive cardiac insufficiency Diseases of peripheral arteries Cerebrovascular disease Dementia Chronic lung disease Connective tissue disease Ulcerative disease Mild hepatic disease Diabetes
2	Hemiplegia Moderate or severe kidney disease Diabetes with organ abnormalities Malignant tumor without metastases Leucemia Lymphoma
3	Moderate or severe hepatic disease
6	Metastatic malignant tumors AIDS (the disease, not only the viremia)
For each 10 years of life after the age of 40 years, add 1 point: 40–49 years — 1 point, 50–59 — 2 points etc.	

Sum of points	10-year survival rate, %
0	99
1	96
2	90
3	77
4	53
5	21

Note. When calculating the Charlson comorbidity index, sum all the age points and the points of somatic diseases. AIDS — acquired immunodeficiency syndrome.

comorbidity, one used the CIRS, another one was employing the weighted Comorbidity Index (w-CI), while the Comorbidity Severity Index (ComSI) and the Complication Severity Index (ComplSI) was used in one research work each. One of the research works based on the Charlson index, had a comparatively small sample (n=58), showing that the Charlson index was one of the several independent predictors for FIM on discharge and FIM during the further follow-up (in an average of 19.5 months) during the multivariate analysis among the groups of patients with cerebellar stroke [24]. Despite the small sample size, not less than seven variables were added to the multifactorial model. The second research included 129 patients and it has shown that the Charlson index was one of the several independent predictors of the functional outcome, influencing on the results of FIM scores on discharge from the in-patient department [9]. Taking into consideration the fact that the Charlson index has not found its wide use in the settings of medical rehabilitation, M. Liu et al. [28] have compiled a new index — the weighted Comorbidity index (w-CI). They have compared the validity and the robustness of their index, which included the complications specific for stroke patients, but not added to the Charlson index, such as the pain in the shoulder, depression and impaired vision, to the Charlson index. When analyzing the FIM values on discharge, the weighted version of their new index, unlike the Charlson index, was the independent predictor for FIM on discharge. G. Ferriero et al. [35] have also compiled a weighted comorbidity index based on the risk factors and the factors limiting the course of medical rehabilitation due to comorbidities. This group has divided the elements of the index compiled by Liu et al. [28], into the comorbidities and the complications of stroke, assigning the scores to functional limitations caused by the comorbidity or by the complication (absence of limitations, moderate limitations and severe limitations), arranging two separate scores for the analysis — the Comorbidity Severity Index (ComSI) and the Complication Severity Index (ComplSI). In this small research work, the patients without comorbidities scored by the ComSI on admission, during the rehabilitation had a higher FIM on discharge comparing to the ones having at least one concomitant disease [35]. In other research work, the Cumulative Illness Rating Scale (CIRS) in a sample of 93 patients did not show any correlation between the CIRS and the FIM on discharge [27].

A large retrospective analysis of the USA data base for the period of 5 years (864 institutions of in-patient rehabilitation) with a huge patient sample (n=371 211) was devoted to evaluating the interrelation between the number of concomitant diseases and the FIM. As a result, a relation was proven between the increase in the number of concomitant diseases (an average of 7.9 concomitant diseases per patient) and the decrease in the probability of achieving or exceeding the rehabilitation objectives (the target FIM value) [31]. Another two large retrospective research works have used the data bases [30, 32] to investigate the role of diabetes severity. Both of them have reported a relation between the severity of diabetes and a lower predictable FIM on discharge in younger population, but did not find a significant interrelation for the elderly patients (older than 80 years), with this, the research works also report the statistically significantly longer

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Table 3

Results of clinical studies when evaluating the rehabilitation potential depending on the comorbidity diseases

Research type	Sample number	Result	Source
Retrospective	58	CCI was an independent predictor of increased FIM on discharge	[24]
Retrospective	129	CCI was one of the several independent predictors for the functional result, determined using the FIM scale, on discharge (corrected for multiple factors)	[9]
Prospective	40	The research has shown that larger number of concomitant diseases negatively affects the final FIM values	[25]
Retrospective	2402	The research did not show clear effects of CCI values on the FIM outcomes, however, the group receiving rehabilitation therapy had better outcomes	[26]
Prospective	93	The CIRS has demonstrated the prediction of concomitant diseases, but not the changes of FIM	[27]
Retrospective	106	w-CI significantly correlated with FIM on discharge and with the duration of hospitalization	[28]
Prospective	1317	The evaluation of the individual concomitant diseases and their effects on the ADL and HADS values has demonstrated a direct negative effect of the number of concomitant diseases on the rehabilitation potential	[29]
Retrospective	135 097	Diabetes (with a large number of complications) correlated with (lower) FIM on discharge and the duration of hospitalization in the younger cohort (<60 years) with a decreasing tendency to the age of 80	[30]
Retrospective	371 211	The increase in the number of comorbidities is related to the decreased chances of achieving the FIM tasks	[31]
Retrospective	35 243	Diabetes (with a large number of complications) correlated with lower predictable FIM on discharge in the younger cohort (<80 years), but not with the duration of hospitalization	[32]
Prospective	97	The presence of several concomitant diseases significantly affects the severity of cognitive disorders acc. to the MoCA and MMSE scores with directly affecting the rehabilitation potential	[33]
Prospective	192	High comorbidity level affected the worse achieving of rehabilitation objectives when evaluating the functions of the upper limb using the ARAT score	[34]
Prospective	85	Low comorbidity level correlates with higher FIM scores on discharge	[35]
Prospective	448	Higher comorbidity level by two validated scales has shown the worst functional outcomes when using the ARAT, TCT (Trunk Control Test), MoCA/MMSE and ADL scales	[36]
Prospective	220	During the multivariate analysis, the younger age along with higher level of functioning, with the lesser number of concomitant diseases, the higher cognitive capabilities and the lesser severity of stroke was associated with higher mBI on discharge	[37]

Note. CCI — Charlson comorbidity index; FIM — Functional Independence Measure; CIRS — Cumulative Illness Rating Scale; w-CI — weighted Comorbidity index; ADL — Activity of Daily Life index; HADS — Hospital Anxiety and Depression Scale; MoCA — Montreal Cognitive Assessment; MMSE — Mini-Mental State Examination; ARAT — Action Research Arm Test; TCT — Trunk Control Test; mBI — the level of mental burnout (modified Barthel index).

in-patient treatment for the elderly individuals (older than 80 years) with more severe diabetes.

In the research work involving 1317 patients, in which data collection was conducted using the primary medical documentation (medical record of an out-patient, form 025/u-04; statistical forms No. 12) and by means of questioning the patients, an interrelation was shown for the severity of comorbidity and the specific rehabilitation scales — Barthell, HADS and the Mini-Mental Status Score. A direct correlation was found

between the presence and the severity of concomitant diseases and the level of rehabilitation potential with the need for evaluating the comorbidity when compiling the individual plan of medical rehabilitation [29]. In other research, the Lithuanian colleagues with a small sample of patients (*n*=40) were using the FIM and MAS (Modified Ashworth Scale) scales to show the direct relationship for the decrease in the rehabilitation results and the severe comorbidity [25].

Interesting results were obtained by H.W. Morrison et al. [33] in a research with the participation of 97 patients, in which a detailed analysis was conducted of the diseases and health conditions in the patients after a history of stroke along with evaluating the status of the higher mental functions using the MoCA and MMSE scores. It was shown that the presence of several concomitant diseases significantly affects the degree of cognitive disorders and directly affects the rehabilitation potential. A quite large research work (*n*=2402) did not find any direct interrelation between the Charlson index score and the changes in the FIM scores, however, the authors themselves have noted the significant heterogeneity in the comparison group, which calls into question the obtained result [26]. In another research that included 192 patients and conducted mainly for the evaluation of the efficiency of the PREP (Predicting Recovery Potential — predicting the restoration of motor functions in the upper limb after a cerebrovascular stroke) algorithm, it was reported that the presence of significant comorbidity was associated with longer stay at the In-Patient Department and with worse functional outcomes during medical rehabilitation [34].

A large prospective research (*n*=448) by A. Finocchi et al. [36] was devoted to the automatization of evaluating the predictors of restoring the possibilities of unassisted moving and included an evaluation of the comorbidity background using the main scores — CIRS-G and Charlson index; the motor and the cognitive functions were evaluated using the validated scales, including the Barthel index, the trunk control test, the Action Research Arm Test (ARAT), the MMSE and the MoCA. As a result, a correlation was found between the higher comorbidity level and the worse functional outcomes to the moment of discharge from the In-Patient Department. In another multicenter prospective observational research [37] involving 220 patients, the authors were arranging a search of the patient assessment algorithm at the early recovery period after an episode of the CVA for the purpose of clearly defining the predictors for the functional outcome. It was determined that comorbidity is an independent and statistically significant prognostic factor, negatively affecting the functional outcome after the intensive rehabilitation, i.e. the higher is the patient's number of concomitant diseases, the lower is the expected level of functional independence on discharge. Also a statistically significant weak negative correlation was found between the CIRS index and the mBI testing result (modified Barthel index) on discharge. After taking into account all the other important factors (age, severity of stroke, motor and cognitive functions on admission), the CIRS index has remained an independent outcome predictor.

CONCLUSION

Evaluating the comorbidities in a patient is one of the most important components of determining the rehabilitation potential after an episode of CVA, directly affecting the choice of the tactics for rehabilitation therapy and its efficiency. The analysis of literature data has shown an interrelation between the number and the severity of the concomitant diseases and the rehabilitation results. Summarizing these data, it can be concluded that the presence of a single concomitant disease such as the hypertensive disease or atrial fibrillation, is the factor, moderately limiting the rehabilitation potential, the presence of diabetes with multiple complications is the factor, significantly limiting the rehabilitation potential and the future restoring the functions, while the presence of two or more significant abnormalities, such as the combination of diabetes and atrial fibrillation, is the predictor for a significant decrease in the rehabilitation potential and for the worse outcome when using the functional independence measure (FIM). Thus, the highest value belongs to severe diabetes with multiple complications, to atrial fibrillation and to chronic cardiac insufficiency with decreased ejection fraction.

Thus, the topical issue is compiling a single unified method of determining the rehabilitation potential.

ADDITIONAL INFORMATION

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FXTAS (Fragile X-Associated Tremor/Ataxia Syndrome)

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ABSTRACT

BACKGROUND: *FXTAS Syndrome (Fragile X-Associated Tremor/Ataxia Syndrome) is a neurodegenerative disease with late onset, which manifests in men and women carrying the mutation in the FMR1 gene, located in the X-chromosome. The disease manifests with high phenotypic variability (tremor, cerebellar ataxia, parkinsonism, oculomotor disorders, cognitive and mental disorders). Due to the insufficient awareness among the physicians on this disease, FXTAS Syndrome patients often get incorrect diagnosis (essential tremor, Parkinson disease, multisystem atrophy, spinocerebellar ataxia etc.).* ***CLINICAL CASE DESCRIPTION:*** *The case presented is the patient aged 68 years with a severe past medical history (ischemic heart disease, post-infarction cardiosclerosis with the formation of post-infarction aneurism, arterial hypertension, pulmonary tuberculosis, chronic obstructive pulmonary disease, type 2 diabetes), in which the FXTAS Syndrome has first manifested with tremors, impaired coordination of motions, balance problems, cognitive disorders and affective disorders. The disease was confirmed by the genetic test (in the FMR1 gene, 96 CGG repeats were found). The patient's daughter was examined with detecting the premutation of the FMR1 gene, while the grandson has a Martin-Bell syndrome.* ***CONCLUSION:*** *Neurologists and specialists of adjacent fields should keep in mind the FXTAS Syndrome (Fragile X-Associated Tremor/Ataxia Syndrome) and, in case of the patient having the corresponding symptoms, should rule out this rare neurodegenerative disease by arranging the genetic testing to reveal the mutation in the FMR1 gene.*

Keywords: *FXTAS syndrome; fragile X-chromosome; tremor; ataxia; neurodegenerative disease; gene; impaired coordination.*

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BACKGROUND

FXTAS Syndrome (Fragile X-Associated Tremor/Ataxia Syndrome) is a rare neurodegenerative disease with late onset, which occurs in the carriers of the mutation in the *FMR1* gene (Fragile X Mental Retardation 1), located in the X-chromosome, and which is related to the increase in the number of CGG (cytosine-guanine-guanine) repeats in this gene [1].

FXTAS Syndrome is considered a rare disease, probably, due to the insufficient diagnostics of this condition. Normally, the number of CGG repeats varies from 5 to 54. An increase in the number of trinucleotides (>200 CGG repeats) results in the impaired synthesis of the FMR1 protein (complete methylation of the gene and loss of the function associated with the synthesis of the FMR1 protein) along with the abnormalities of developing the nervous system — the Martin-Bell syndrome or mental deficiency syndrome associated with the fragile X-chromosome [2, 3]. The condition, in which the number of CGG repeats is more than normal values (>55), but it does not exceed the threshold value (>200 CGG repeats), is generally called the premutation. The premutation may manifest as four various disorder profiles:

1) childhood age development disorders (non-rough deviations of the cognitive development, autistic spectrum disorder, attention deficit and hyperactivity syndrome);
2) impaired reproductive functions and other somatic problems in women (primary ovarian insufficiency syndrome, hypothyroidism);
3) neurodegenerative disorders at the old age (tremor and ataxia syndrome, or FXTAS, more often in men);
4) psychoemotional problems (depression, anxiety disorders, obsessive-compulsive disorder) [2].

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Синдром FXTAS (тремор/атаксия, ассоциированные с ломкой Х-хромосомой)

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АННОТАЦИЯ

Обоснование. *Синдром FXTAS (Fragile X Associated Tremor/Ataxia Syndrome) — нейродегенеративное заболевание с поздним началом, которое возникает у мужчин и женщин, являющихся носителями мутации в гене FMR1, расположенном на хромосоме Х. Заболевание проявляется высокой фенотипической вариабельностью (тремор, мозжечковая атаксия, паркинсонизм, глазодвигательные расстройства, когнитивные и психические нарушения). Вследствие недостаточной осведомлённости врачей о данной патологии пациентам с синдромом FXTAS часто ставят неправильный диагноз (эссенциальный тремор, болезнь Паркинсона, мультисистемная атрофия, спиноцеребеллярная атаксия и др.).* ***Описание клинического случая.*** *Представлен пациент в возрасте 68 лет с тяжёлым анамнезом (ишемическая болезнь сердца, постинфарктный кардиосклероз с формированием постинфарктной аневризмы, артериальная гипертензия, туберкулёз лёгких, хроническая обструктивная болезнь лёгких, сахарный диабет 2-го типа), у которого синдром FXTAS дебютировал с тремора, нарушения координации движений, проблемы равновесия, когнитивных расстройств и аффективных нарушений. Заболевание подтверждено генетическим анализом (в гене FMR1 обнаружено 96 повторов CGG). У дочери пациента выявлена премутация гена FMR1, у внука — синдром Мартина–Белл.* ***Заключение.*** *Врачам-неврологам и специалистам смежных областей следует помнить о синдроме FXTAS (тремор/атаксия, ассоциированные с ломкой Х-хромосомой), и при наличии у пациента соответствующей симптоматики исключить редкое нейродегенеративное заболевание путём генетического исследования мутации в гене FMR1.*

Ключевые слова: *синдром FXTAS; ломкая Х-хромосома; тремор; атаксия; нейродегенеративное заболевание; ген; нарушение координации.*

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FXTAS Syndrome starts to 50 years of age and older with an incidence rate in the whole population being 1/1000–2000 males. FXTAS Syndrome is more commonly seen in men comparing to women, which is related to the mechanism of inheritance, for men have only one X-chromosome, due to which they are more prone to this mutation. The presence of the second X-chromosome in women compensates the pathological allele of the *FRM1* gene [4]. With the aging, the probability of clinical manifestations of the FXTAS Syndrome increases, which emphasizes the importance of monitoring the health status of the carriers of the pathological allele after the age of 50 years [4].

The pathogenesis of FXTAS Syndrome is multifactorial. First of all, the basis of the FXTAS pathogenesis has the neurotoxicity aspect due to the forming non-coding ribosomal RNA with elongated CGG sequences, which affect the functions of various proteins, which, in turn, causes the impairment in the functions and the apoptosis of neurons [5]. Secondly, the mitochondrial dysfunction due to the expansion of CGG results in the impaired energy metabolism in the cells and the generation of free radicals. These metabolic disorders may contribute to neurodegeneration. Third off, the, inflammatory processes with high level of inflammatory markers in FXTAS patients negatively affect the neurovascular interaction and the neuroplasticity. In addition to that, the activity of certain genes and proteins, participating in the protection of neurons from stress, can be altered in FXTAS Syndrome patients, which promotes to the

increase in the sensitivity of neurons to damaging factors [5–10].

In adults, the clinical manifestations of FXTAS usually begin after 50 years of age, more often with kinetic tremors, and later on, the elements of cerebellar ataxia join [3]. The disease manifests with high phenotypic variability, for among the clinical signs, besides tremors and cerebellar ataxia, there could be the parkinsonism syndrome, the oculomotor and cognitive disorders, as well as the affective changes, such as depression and agitation [8]. Some patients can have complaints of sleep disorders and changes in the emotional aspects [9].

The carriers of the mutations in the *FMR1* gene, located at the X-chromosome, can have concomitant cerebrovascular abnormalities and other neurological diseases, such as Parkinson's disease and other disorders, which complicates the diagnostics [11]. The diagnostics of FXTAS Syndrome includes several key stages. Thus, the important aspect is the collection of the anamnestic data, which allows for detecting the presence of tremors and impaired coordination, including similar symptoms among the close relatives. Within the family, where previously there were cases of the fragile X-chromosome syndrome, the probability of the presence of FXTAS in older age men is especially high. The confirmation of the diagnosis requires the fragmental analysis of the *FMR1* gene for the purpose of detecting the elongated CGG sequences.

In FXTAS Syndrome patients, the obligatory procedure is performing the magnetic resonance imaging (MRI) examination for the evaluation of the neurodegenerative process in the brain. The main diagnostic signs in the brain MRI images are the impairment of the white matter in the middle crus of cerebellum and the decrease in the volume of the cerebellum, leading to the impaired coordination of motions; changes within the white matter expressed as the hyperintensive areas revealed using the mode of T2-weighted images, especially in the area of the frontal and the occipital lobes; atrophic changes in other areas of the central nervous system, in particular, the subcortical structures and the brain stem. Besides, specific is the presence of microstructural changes, detectable by using the special MRI sequences [12].

At the present moment, there is no therapy specific for the FXTAS Syndrome. Symptomatic therapy is used, aimed at minimizing the clinical manifestations. The important aspect of treatment is the personified rehabilitation therapy for improving the motor skills and the cognitive functions [13].

The prognosis in FXTAS Syndrome patients depends on many factors, including the age, in which the correct diagnosis was set, the degree of severity of symptoms, as well as the individual specific features of developing diseases and the treatment response. Though FXTAS Syndrome is a progressive disorder, the rate of progression is individual, and many patients can maintain the acceptable quality of life for many years. Eventually, however, the majority of patients develop an aggravation in their motor functions and cognitive capabilities. The diagnosis of FXTAS Syndrome is confirmed by the genetic counseling of the family members and by the detection of mutation in the *FMR1* gene.

CLINICAL CASE DESCRIPTION

Patient information

Patient B., aged 68 years, Russian, higher education, admitted for in-patient treatment at the State Budgetary Healthcare Institution of the Tyumen Oblast "Regional Clinical Hospital No. 1" in February 2025 with the complaints of tremors in the left palm, anxiety, agitation and fatigability.

Case history. Approximately two years ago, the first signs of mild transient tremor in the left arm have appeared. According to oral information provided by the patient, the worsening of the conditions started several months ago (18.10.2024), when he fell and hit his head (the reason of falling cannot be explained by the patient). No encounter for medical aid followed. The patient's wife notes that recently he became "retarded and suspicious", stopped walking outside, explaining it by the absence of any will to do so.

On 01.11.2024, in the morning he could not get up from his bed, had an episode of dizziness with developing weakness in the whole body, especially in the lower limbs, after which he fell. At the In-Patient Department, Brain MRI was conducted using the diffusion-weighted mode (Diffusion Weight Imaging, DWI): symmetrical signal increase from the corticomedullary junction of the brain hemispheres, from the fibers of the corpus callosum and from the substance of the middle peduncles of the cerebellum (Fig. 1).

On 28.01.2025 the patient was consulted by the Geneticist (with testing for the presence of the expansion of CGG-repeats in the *FMR1* gene): pre-expression of CGG-repeats was found — 96/0. Increased risk of developing the tremors-ataxia syndrome.

Past medical history. Ischemic heart disease. Post-infarction cardiosclerosis with the formation of

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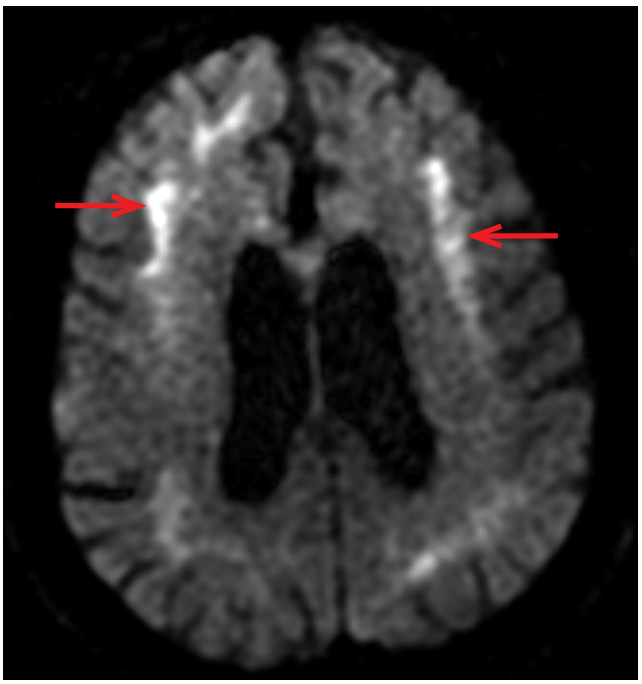

Fig. 1. Symmetrical DWI-hyperintensity at the level of the corticomedullary junction on both sides at the frontal (arrows) and parietal lobes.

post-infarction aneurism (ejection fraction — 40%). In 2022 the patient underwent stenting of the heart vessels.

The blood pressure had a long period of maximal values of 150/90 mm.Hg. (he is taking Uperio, Torasemide, Bisoprolol, Atorvastatin and Cardiomagnyl).

In 2023 the patient had an episode of pulmonary tuberculosis. Long-term history of medical supervision with chronic obstructive pulmonary disease and with type 2 diabetes (taking Empagliflozin).

Laboratory and instrumental diagnosis

Neurological status. The general status is satisfactory. Active body position. Clear consciousness. The general cerebral symptoms are uncertain. The oculomotor nerves are unremarkable. Hypomimia. The face is symmetrical. Primitive oral reflexes detected: snout reflex, palm-chin reflex (Marinescu sign) on both sides. The muscle strength in the limbs is sufficient, except for decreased strength in the arm on the left side down to 4 points. The muscle tone in the proximal and the distal areas is increased following the extrapyramidal pattern, more on the left side. The reflexes in the limbs (D=S) are increased. Pathological plantar reflexes — negative. Tremors in the head (the "no-no" type), in the tongue, mild postural tremor in the trunk. Periodical myoclonic twitching in the left palm, right-sided body deviation when standing and walking (the Pisa syndrome). The Romberg stance test shows a deviation to the right. Finger-to-nose test — hesitant due to kinetic tremors, more on the left side. The gait has signs of mild ataxia. Retropulsion. The superficial and the deep sensorial functions are intact.

General (clinical) hematology panel (04.02.2025): leucocytes (WBC) 8.81×10^9/l; Red blood cells (RBC) 4.52×10^{12}/l; hemoglobin (HGB) 134 g/l; platelets (PLT) 237×10^9/l.

The *blood biochemistry panel* and the *ion profile* show no abnormalities, except for creatinine level elevated up to 115 μmol/l.

Electroencephalography (05.02.2025) — no signs of paroxysmal activity.

Fundoscopy (04.02.2025): retinal angiopathy in both eyes.

Brain MRI (05.02.2025): the observations include a diffuse inhomogeneous increase of the MRI-signal from white matter of the brain for T2- and T2-FLAIR (Fluid-Attenuated Inversion Recovery) images with spreading to the middle cerebellar peduncles and the cerebellum hemispheres, with linear-stellar increase of the MRI-signal for the DWI mode, with no signs of diffusion restriction. Conclusion: "MRI signs corresponding to the manifestations of the neurodegenerative diseases (FXTAS). Diffuse cerebral atrophy grade I" (Fig. 2, 3).

Consultation by the psychologist (05.02.2025). Using the method by A.R. Lauria, 3 words out of 10 were learned, after a period 40 minutes, the test subject has reproduced one world (ref. range: 5–7 words). The data indicate the intensive impairment both in the short-term and in the long-term memory. The motivational component of the memory is decreased. The speed of mental activity is slowed. The rate and the tempo of the associative process corresponds to the lower reference range; deviations were detected in the dynamic mental activity, expressed as the slower association rate, decreased mobility and passivity of thinking.

Moderate cognitive disorders were determined using the Mini-Mental State Examination score (MMSE, 24 points) with moderate sleep disorders according to the Spiegel scale (15 points), with extremely severe asthenia according to the subjective scale for asthenia (Multidimensional Fatigue Inventory, MFI, 20–84%), clinical anxiety according to the Hospital Anxiety and Depression Scale (HADS, 15 points).

Diagnosis

Based on the disease history data, on the data from neurological and neuropsychological

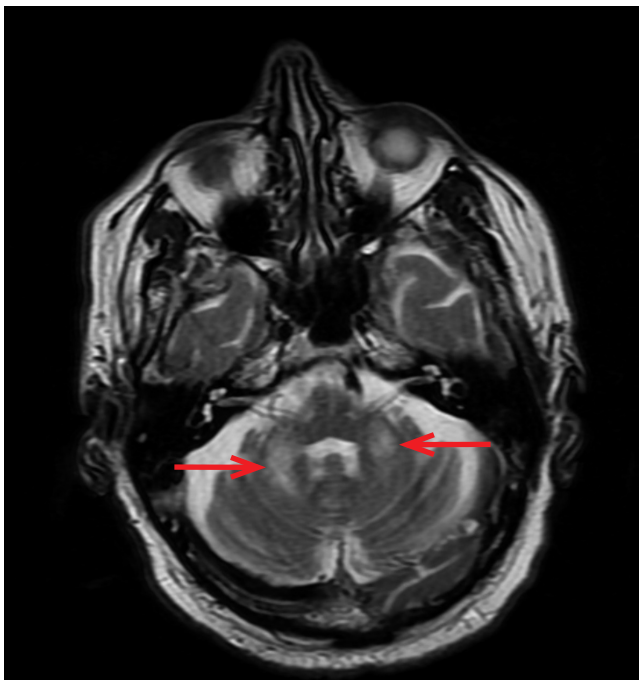

Fig. 2. Symmetrical foci of high signal in the T2-weighted images at the level of the middle cerebellar peduncles.

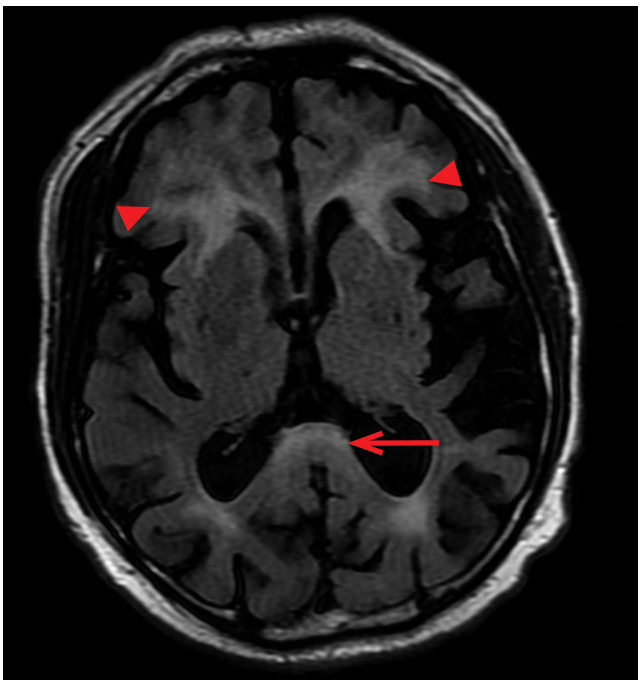

Fig. 3. Hyperintensity in the area of the splenium of corpus callosum in a series of FLAIR (long arrow), additional finding — foci of symmetrical periventricular leukoaraiosis near the anterior horns (short arrows).

examination, from the genetic and the instrumental diagnostics, the following clinical diagnosis was set: "Neurodegenerative disease of the nervous system, tremors/ataxia syndrome, associated with the fragile X-chromosome syndrome (FXTAS). Mild paresis in the left upper limb. Parkinsonism syndrome. Mixed (postural, kinetic) resting tremor, more on the left side, myoclonus in the left palm. Mild ataxic syndrome. Syndrome of cognitive disorders. Pronounced asthenic and anxiety syndromes".

Treatment

At the in-patient stage, the patient was receiving neurometabolic therapy: choline alfoscerate, ethylmethylhydroxypyridine succinate, group B vitamins.

Follow-up and outcome

The patient was discharged from the In-patient Department on Day 7 for out-patient follow-up by the Neurologist at place of residence. The neurology status was showing no significant changes. The recommendations included the cognitive training sessions, the metabolic therapy cycle along with arranging the genetic testing of blood relatives for the presence of fragile X-chromosome and FXTAS Syndrome. Repeated hospitalization was scheduled in 6–9 months for the purpose of an appraisal of clinical signs and for the correction of therapy.

DISCUSSION

The differential diagnostics of the FXTAS Syndrome is a complex process. The disease manifests with high phenotypic variability (tremor, cerebellar ataxia, parkinsonism, oculomotor disorders, mental disorders). Taking into consideration the insufficient awareness among the physicians regarding this disorder, the patients are often managed with other diagnoses (Essential tremor, Parkinson disease, multisystem atrophy, spinocerebellar ataxia etc.). The treatment of the FXTAS Syndrome is mainly symptomatic, aimed at the improvement of coordination, and cognitive functions with decreasing the affective manifestations.

The main diseases to be differentiated with the FXTAS Syndrome are the Parkinson disease and the parkinsonism syndrome. Though both these conditions can include tremors and motor disorders, in Parkinson's disease, the patients usually have the characteristic symmetrical rigidity of muscles, as well as tremors at rest, which is absent in FXTAS Syndrome patients, additionally, the MRI scans in Parkinson's disease patients can show other changes, such as the loss of dopaminergic neurons in the black substance [8, 14, 15]. The national literature contains a single clinical

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case of the FXTAS Syndrome in a male aged 58 years manifesting as the combination of asymmetrical disabling postural-kinetic tremors in the upper limbs, insignificant resting tremors, moderate cerebellar ataxia, asymmetrical moderate DOPA-sensitive parkinsonism syndrome, mild cognitive impairment and psychotic disorders. In the daughter of the patient presented, a premutation was found in the *FMR1* gene, in the grandson — the Martin-Bell syndrome was detected. The specific feature of the clinical case was the long-term erroneous following-up the patient with the diagnosis of Parkinson disease, including the treatment with high dosages of Levodopa/Carbodopa (250+25 mg, up to 6 tablets daily) [3].

When conducting the differential diagnostics with the demyelinating diseases of the brain, in particular, with multiple sclerosis, which also may cause ataxia and tremors, our patient had no detected changes in the visual perception and paresthesias, while the Brain MRI does not show demyelination foci within the white matter [16].

No less than important is ruling out the variant of the Huntington's disease, which often leads to motor dysfunction and cognitive disorders. The Huntington's disease, unlike the FXTAS Syndrome, has its clear intensive genetic markers and includes the psychiatric symptoms [17].

CONCLUSION

Exploring the FXTAS Syndrome is extremely important and topical for modern scientific and medical communities. The diagnostics of FXTAS Syndrome requires the thorough reviewing of the family history, the analysis of clinical symptoms with the neurovisualization results and arranging the genetic testing. Timely genetic testing for detecting the mutation in the *FMR1* gene allows for providing the symptomatic therapy and rehabilitation, which is an important factor in maintaining the quality of life for the FXTAS Syndrome patients.

ADDITIONAL INFORMATION

Author contributions: *E.S. Ostapchuk*, review of publications on the topic of the article, scientific editing of the article; *M.V. Malakhov*, performance and description of radiation diagnostics, review of publications on the topic of the article; *Yu.S. Morozova*, description of a clinical case, review of publications on the topic of the article; *V.V. Kuznetsov*, *S.S. Chikviladze*, treatment of the patient, correction of the manuscript part of the text. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication: The authors received written informed voluntary consent from the patient to publish personal data, including photographs (with the face covered), in a scientific journal, including its electronic version (signed on 2025 Feb 14). The volume of published data was agreed upon with the patient.

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Bilateral Tibial Lesions as an Onset of the Diffuse B-Cellular Non-Hodgkin Lymphoma

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ABSTRACT

BACKGROUND: *Diffuse B-cellular non-Hodgkin lymphoma is the most widespread in this group of diseases, causing the highest number of lymphoma-related lethal outcomes worldwide. The clinical-pathological heterogeneity of the nosology negatively affects the possibilities of precise and timely diagnostics. The variety of extranodal locations of the disease requires the participation of a multidisciplinary team of high qualification specialists, the use of high-tech methods for diagnostics and the aggressive therapy. The article presents a discussion on the occurrence of the diffuse B-cellular non-Hodgkin lymphoma, on the rates of an onset with the lesions in the skeleton, on the specific features of the disease course that is mimicking the rheumatic disease, as well as on the difficulties of recognizing it due to the absence of specific symptoms at the beginning of the disease and to the necessity of using high-tech instrumental diagnostic methods.* ***CLINICAL CASE DESCRIPTION:*** *The article presents a clinical case of the patient aged 57 years, hospitalized to the Regional Tuberculosis Dispensary with the provisional diagnosis of tuberculosis-associated arthritis of the ankle joints. At the out-patient phase, the differential diagnostics was conducted between the inflammatory disease of the joints, the trauma, the bone tuberculosis and the orthopedic abnormalities. The radiology image of the chest cavity organs showed the presence of diffuse pneumosclerosis, according to the data from multispiral computed tomography, a cystic transformation was found along with the space-occupying mass lesions and osteolysis in the distal areas of both tibial bones. Based on the results of the histological examination of the lower third of the left tibia, a diagnosis of diffuse B-cellular non-Hodgkin lymphoma with high proliferative activity was set, confirmed at the specialized medical institution using the method for calculating the IPI prognostic index (International Prognostic Index).* ***CONCLUSION:*** *The presented case demonstrates the necessity for oncological alertness and for multidisciplinary approach for ruling out the primary and the secondary non-Hodgkin lymphomas of bone tissue location, mimicking the bilateral disease of the joints, for the purpose of early diagnostics and timely treatment, improving the prognosis for patients with this group of diseases.*

Keywords: *B-cell non-Hodgkin lymphoma; diagnosis; rheumatic diseases.*

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BACKGROUND

The diagnostics of lymphoid tissue tumors represents a complex task for the clinicist, which is due to the variety of nosologies in this group of diseases, many of which have a course mimicking other pathologies. Diffuse B-cellular large cell lymphoma differs by the aggressive clinical course with a tendency to rapid growth and early progression, as well as high sensitivity to chemotherapy. The occurrence rate reaches 40% of all the non-Hodgkin lymphomas. The incidence rate of diffuse B-cellular large cell lymphoma is 4–5 cases per 100 thous. of population. Every year worldwide, approximately 120 thous. of new cases are diagnosed. The diseases affect predominantly males with peak of incidence after 60 years of age [1, 2]. Currently, the clinical cases were described in which the course of lymphomas included the initial lesions in the liver, the heart, the mediastinum, the testicles or the central nervous system [1, 3, 4]. Non-Hodgkin lymphomas most commonly have a B-cellular origin [5].

Multiple research works have determined the interrelation between the autoimmune diseases and

Двустороннее поражение большеберцовых костей как дебют диффузной В-клеточной неходжкинской лимфомы

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АННОТАЦИЯ

Обоснование. *Диффузная В-клеточная неходжкинская лимфома является наиболее распространённой в данной группе заболеваний, вызывающих самое высокое в мире число смертей, связанных с лимфомами. Клинико-патологическая гетерогенность нозологии отрицательно влияет на возможность точной и своевременной диагностики. Разнообразие экстранодальной локализации заболевания требует участия мультидисциплинарной бригады специалистов высокой квалификации, применения высокотехнологичных методов диагностики и агрессивной терапии. В статье обсуждается распространённость диффузной В-клеточной неходжкинской лимфомы, частота дебюта с поражения скелета, особенности течения под маской ревматического заболевания, а также трудности распознавания ввиду отсутствия специфических симптомов в начале болезни и необходимости использования высокотехнологичных инструментальных методов диагностики.* ***Описание клинического случая.*** *В статье представлен клинический случай пациента в возрасте 57 лет, госпитализированного в областной противотуберкулёзный диспансер с предварительным диагнозом туберкулёзного артрита голеностопных суставов. На амбулаторном этапе дифференциальный диагноз проводился между воспалительным заболеванием суставов, травмой, туберкулёзом костей и ортопедической патологией. По рентгенограмме органов грудной клетки выявлен диффузный пневмосклероз, по данным мультиспиральной компьютерной томографии — кистозная перестройка, объёмные образования и остеолиз дистальных отделов обеих большеберцовых костей. По результатам гистологического исследования нижней трети левой большеберцовой кости выставлен диагноз диффузной В-клеточной неходжкинской лимфомы с высокой пролиферативной активностью, подтверждённый в профильном медицинском учреждении методом расчёта прогностического индекса IPI (International Prognostic Index).* ***Заключение.*** *Представленный случай демонстрирует необходимость онкологической настороженности и мультидисциплинарного подхода для исключения первичных и вторичных неходжкинских лимфом костной локализации, имитирующих двустороннее заболевание суставов, с целью ранней диагностики и своевременного лечения, улучшающего прогноз для пациентов с этой группой заболеваний.*

Ключевые слова: *В-клеточная неходжкинская лимфома; диагностика; ревматические заболевания.*

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the high rate of developing B-cellular lymphomas. The highest risk of non-Hodgkin lymphoma was observed in cases of Sjogren disease, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, dermatomyositis, polymyositis and Still syndrome [4–6]. The process of differential diagnostics for such conditions sometimes takes up to two years, which determines a significant delay of adequate therapy [7]. The most frequent locations of primary non-Hodgkin lymphomas are the femoral and tibial bones, the pelvic bones, the vertebrae and the ribs. The predominant findings are the osteolysis foci or a combination of lytic and sclerotic changes [8]. The tumor tissue often contains foci of necroses and of accumulating atypical cells. The process is accompanied by thinning of the spongy and of the compact bone tissue [8–11].

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Here we present a clinical case of the B-cellular non-Hodgkin lymphoma patient with bilateral lesions in the distal areas of the tibial bones, by its onset mimicking the rheumatic disease.

CLINICAL CASE DESCRIPTION

Patient info

Patient S., aged 57 years.

Case history. In autumn of 2018 he started feeling pain in the area of the ankle joints, increasing with movements, and swelling in the ankle joints. He was repeatedly consulted by the surgeon with such manifestations being estimated as the complications of chronic ischemia in the lower limbs. Taking into consideration the past medical history of the patient (in 2017 — thrombosis of the aneurism in the popliteal artery with the development of acute ischemia, femoropopliteal autovenous prosthetic replacement), this version was considered the top-priority one. The patient was referred to the vascular surgery specialist, underwent ultrasound duplex scanning, as a result of which, a conclusion was drawn that the circulation in the arteries of the lower limbs was compensated. At the out-patient phase, the differential diagnostics also was carried out between the inflammatory disease of the joints, the trauma, the bone tuberculosis and the orthopedic abnormalities. The vascular surgery specialist, the rheumatologist and the orthopaedist have ruled out the presence of specific abnormalities.

For several months, the severity of symptoms was progressing, the patient was not able to move without assistance because of pain. He was then consulted by the phthisio-orthopaedist and hospitalized to the Regional Tuberculosis Dispensary with the following provisional diagnosis: “Tuberculosis-associated arthritis of the ankle joints, congestive peri-articular abscesses, severe pain syndrome”.

Past medical history. Growth and development according to the age. Living at a well-furnished apartment, the living conditions are satisfactory. Contact with tuberculosis patients — negative (verbal information provided by the patient). Smoking approximately one pack a day for many years. In 2015 — pacemaker implantation (ischemic heart disease, sick sinus node syndrome, atrial fibrillations, paroxysmal form, normosystole). Suffers from the obliterating atherosclerosis in the arteries of the lower limbs, chronic ischemia of the left lower limb stage IIb, in 2017 — surgery operated — femoropopliteal autovenous by-pass grafting on the right side. Group III disability according to the general disease.

Laboratory and instrumental diagnosis

On admission the state of the patient has moderate degree of severity. Body position — sitting on his bed. The skin and the visible areas of mucosal membranes are pale-pink and moistened. At the internal surface from the middle third of the right thigh to the middle third of the right shin, there is a postoperative scar. The subcutaneous-fatty tissue and the muscular system are satisfactorily developed. The occipital, the parotid, the submandibular, the submental, the cervical, the supraclavicular, the subclavian, the subpectoral, the axillary, the cubital, the inguinal, the femoral and the popliteal lymph nodes are not palpable, the skin above them is unremarkable. The chest has a correct shape, being symmetrical and painless, with both halves participating in the respiratory movements, the percussion of the lungs reveals a clear pulmonary percussion sound. The auscultation reveals vesicular breathing without any abnormal respiratory sounds. The respiratory rate is 16/minute. The heart projection area visually has no abnormalities, the cardiac rhythm is correct, the heart tones are clear and the heart rate is 76 bpm. Blood pressure — 120/80 mm.Hg. in both arms. The tongue is clear and moistened. The abdomen is participating in respiratory movements, soft and moderately painful in the right hypochondrium; the liver on palpation is located near the margin of the right costal arch. The kidneys and the spleen are not palpable; the costovertebral tenderness test in the lumbar area is negative on both sides. The urination and stools show no abnormalities.

Local status: the skin in both feet is hyperemic, densified and swollen (more on the left side), the swelling is spreading to the middle third of the shin. The active and passive motions in the ankle joints are significantly limited due to the sensation of pain. The axial load is sharply painful. The peripheral pulsation in the foot arteries is weakened, more on the left side. Smoothened contours of the medial malleolus on the left side, the palpation reveals a non-dislocatable tumor lesion with doubtful deviation of its dimensions from the normal ranges, the skin above it has a dark-crimson shade, being warm.

Laboratory examination. The clinical tests of blood and urine samples dated 17.05.2019 were normal. Sputum microscopy in search of Mycobacteria tuberculosis: the result was negative. The microprecipitation reaction was also negative. No antibodies were detected to human immunodeficiency virus, as well as the markers of hepatitis B or C. The blood biochemistry panel values (parameters: glucose,

transaminases, bilirubin, total protein, creatinine, urea) were also within the normal ranges.

Instrumental examination. Multispiral computed tomography on 12.05.2019: cystic transformation, volume-occupying mass lesions and osteolysis in the distal areas of both tibial bones (Fig. 1). Chest cavity X-ray dated 16.05.2019: diffuse pneumosclerosis. Ultrasound examination of the abdominal cavity organs dated 20.05.2019: no signs of structural abnormalities.

Diagnosis

On 28.05.2019, in the settings of the Regional Tuberculosis Dispensary, the patient underwent an open-access biopsy of the lower third of the left tibial bone. The conclusion from the protocol of intra-vitam pathology examination was the following: "The examined sample contains a fragment of the bone tissue, in which the findings include a hypercellular infiltrate of large lymphocyte-like cells with light-colored nuclei. Upon the immunophenotyping with using the CD20 marker (×100) — significant expression was found in all the tumor cells, Ki-67 (×100) — nuclear expression in 60–70% of the tumor cells, high proliferative activity. Small fragments of grey-brown tissue, the histological examination reveals a diffuse hypercellular infiltrate of large lymphoid cells with light-colored nuclei, with the presence of nucleoli and of small lymphoid cells. Diffuse B-cellular large cell non-Hodgkin lymphoma with high proliferative activity".

Treatment and outcome

The patient was hospitalized to the specialized medical institution, where, using the calculated IPI prognostic index (International Prognostic Index), developed for predicting the outcome in patients with aggressive non-Hodgkin lymphoma, he was confirmed as having a high risk of lymphoma and polychemotherapy cycles were prescribed.

Sadly, but, despite the conducted therapy, the status of the patient has progressively worsened, and in several months the patient has deceased. Such an outcome, probably, was resulting from the presence of several risk factors for unfavorable prognosis, including the age, the extranodal (i.e. localizing in the internal organs) location of the lymphoma, its aggressive clinical course with a tendency to rapid growth and early progression, high IPI risk, high proliferative activity index in the tumor cells (Ki-67). There is an opinion stating that the increase of the Ki-67 specific protein concentration by more than 20% leads to the worsening of the prognosis and to the increases probability of developing a recurrence [10, 11].

DISCUSSION

The bony skeleton in cases of non-Hodgkin lymphoma gets involved in more than 25% of the cases of metastatic spreading or even less frequently in cases of primary bone lymphoma.

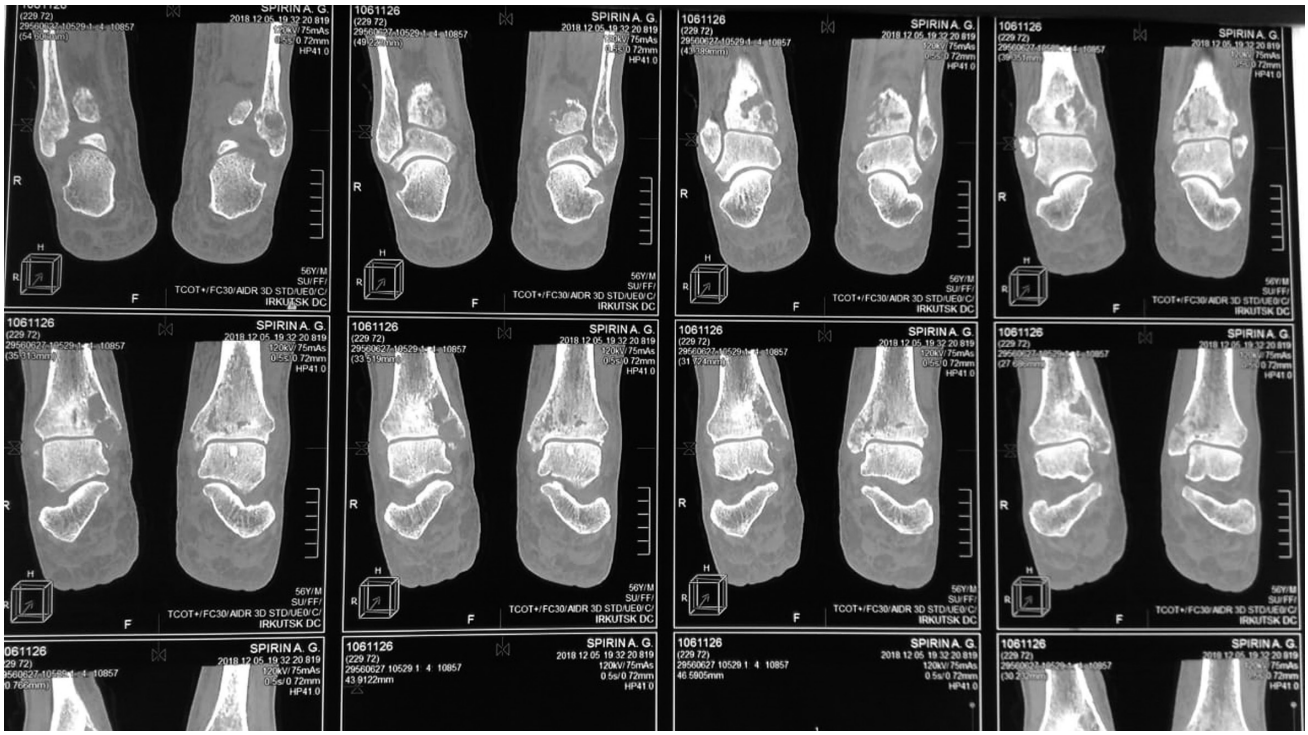

Fig. 1. Multispiral computed tomography: osteolytic destructive changes in the distal areas of the tibial bones.

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Primary non-Hodgkin lymphoma in the bone tissue may cause multiple osteolytic lesions in the skeleton, in particular, in the lower limbs, the pelvis and the vertebral column [9, 11–15]. The cases were described that involve the cranial bones, the orbit, the upper or lower jaws [16–19]. Non-Hodgkin lymphoma occurs infrequently, which is why it is rarely included into the differential-diagnostic search in cases of osteolytic tumors, besides, the primary non-Hodgkin lymphoma can be misdiagnosed due to the absence of symptoms or objective changes in the patients at early stages, being detected, for example, in cases of pathological fractures developing as a result of falling in elderly patients [19]. In the absence of peripheral lymphadenopathy and lesions in the internal organs, the diagnosis of non-Hodgkin lymphoma can be set only as a result of histological examination. During its onset, the non-Hodgkin lymphoma can mimic a rheumatic disease, which is confirmed by the clinical case described above. The foreign literature describes 17 cases of non-Hodgkin lymphoma with the course mimicking the mono- or polyarthritis [9, 12, 19]. Most frequently, lesions were located in the elbow or the knee joints, and only 3 patients had the presence of general symptoms (loss of body weight, weakness, nighttime sweating, fever with chills). In the majority of cases, the involvement of joints was the early manifestation of the disease, and the data from magnetic resonance tomography were showing signs of a non-specific inflammatory process in the joints [20]. The clinical observation presented above is interesting by its symmetrical location of the pathological process. The literature has the descriptions of cases of bilateral lesions in the bones of the lower limbs with their “disappearance”, i.e. osteolysis. Also known is the possibility of bilateral location of the pathological process in the adrenal glands, the urinary ducts and the testicles with a rapid development of severe functional disorders. It is recognized that in case of diffuse B-cellular large cell lymphoma, bilateral symmetrical location of the process, both in the bones and extranodally, occurs rarely [20, 21]. Primary bone lymphoma represents not more than 2% of all the non-Hodgkin lymphomas in adult patients [20–22]. The detected findings are the defects in one or more bones, with the possible involvement of the regional lymph nodes and of the soft tissues. The disease starts with pain syndrome with local swelling and developing tumor masses in the affected area. Most commonly, the diaphyses of the long tubular bones get involved [22–24].

The difficulties of diagnostics in this case are related not only to the low incidence of non-Hodgkin lymphoma, but also to the absence of symptoms usually associated with the oncological disease [25].

CONCLUSION

The presented case demonstrates the necessity of oncological alertness and of the multidisciplinary approach for the purpose of ruling out the primary or secondary non-Hodgkin lymphomas with bone tissue location, imitating the bilateral disease of the joints, for the purpose of early diagnostics and timely treatment, for improving the prognosis in patients with this group of diseases.

ADDITIONAL INFORMATION

Author contributions: *M.V. Karnakova*, creation of a research concept, preparation of a draft article; *I.V. Andryushchenko*, *D.V. Belykh*, conducting research; *A.N. Kalyagin*, revision and editing of the article. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication: The authors received written informed voluntary consent from the patient to publish personal data, including photographs (with the face covered), in a scientific journal, including its electronic version (signed on 2019 May 16). The volume of published data was agreed upon with the patient.

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The First Experience of Conducting the Anesthetic Support During a Simultaneous Surgery in a Kindler Syndrome Patient

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ABSTRACT

BACKGROUND: *Kindler syndrome is a rare autosomal recessive disease, one of the forms of congenital epidermolysis bullosa. Clinically, the disease manifests by the development of bubbles on the skin and mucosal membranes with further cicatrization, as well as by the development of narrowing in the esophagus, the urethra, the vagina and the urinary ducts. In the presented clinical case of the first ever in Russia conducted simultaneous surgery in the settings of general combined anesthesia in a patient with Kindler syndrome, evaluation was carried out for the criteria of difficult airways, special attention was paid to the method of conducting the endotracheal intubation, to monitoring the vital functions of the organism and to following the multimodal analgesia principle. Due to the high risk of post-operative nausea and vomiting, a necessity was justified for increasing the antiemetic effect.* ***CLINICAL CASE DESCRIPTION:*** *The main indications to conducting the surgery in a female patient aged 49 years with congenital epidermolysis bullosa (Kindler syndrome) were the complaints of significant difficulties and pain upon swallowing, decreased appetite, presence of dysphagia with a background of inhomogeneous circular narrowing of the esophagus, pain when moving the eyes and the absence of nasal breathing with a background of nasal vestibule atresia. The main tasks of surgical treatment were the elimination of incapacitating complications and improving the quality of life for the patient. The multiplicity of stages in the treatment process was deemed impractical due to the necessity of conducting three anesthetic support procedures with high risk of additional damaging the oropharynx and upper airways during tracheal intubation, due to which, a decision was drawn up on arranging a simultaneous surgical treatment of complications of the main disease. The duration of surgery was 195 minutes, while the anesthesia lasted for 210 minutes. The performed procedures included the elimination of eyelid eversion, the dissection of symblepharon, the excision of the nasal vestibule atresia and the endoscopic dilation of esophageal stricture. The postoperative period was uncompromised with reported restoring the functioning of nasal breathing, of the visual organs and with the elimination of dysphagia. Upon the examination conducted 11 months after surgery, there were no signs of recurrence of the eliminated complications of the main disease.* ***CONCLUSION:*** *Increasing the safety and preventing the iatrogenic complications during the course of anesthesia in patients with epidermolysis bullosa is the most important task. The development of modern medical technologies with using the microsurgical and the endoscopic methods along with the personalized approach in selecting the anesthetic support allow for wider usage of simultaneous surgeries in the treatment of complications in Kindler syndrome patients.*

Keywords: *Kindler syndrome; epidermolysis bullosa; difficult airways; general anesthesia; stricture dilation; endoscopic balloon dilation.*

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BACKGROUND

Kindler syndrome is one of the four types of congenital epidermolysis bullosa, being a very rare autosomal recessive genodermatosis. As of today, in the whole world, there are approximately 400 registered cases of the disease [1]. Among the main clinical manifestations of this disease are the formation of bubbles on the skin and the mucosal membranes from the moment of birth after a minimal injury, generalized progressive poikiloderma, photosensitivity, pseudosyndactyly, narrowing of the esophagus, of the urethra, of the vagina and of the urinary ducts, as well as colitis and esophagitis [2]. The often reported signs include the dystrophy of nail plates, the ectropion in the lower eyelids, keratoderma, fibrotic finger constrictions, impaired sweating (anhidrosis or hypohidrosis), leukokeratosis of the lips, ulcers in the buccal mucosa and in the hard/soft palate [3].

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Первый опыт проведения анестезиологического пособия при симультанной операции у пациентки с синдромом Киндлера

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АННОТАЦИЯ

Обоснование. *Синдром Киндлера — редкое аутосомно-рецессивное заболевание, одна из форм врождённого буллёзного эпидермолиза. Клинически заболевание проявляется образованием пузырей на коже и слизистых оболочках с последующим рубцеванием, а также развитием сужений пищевода, уретры, влагалища и мочеточников. В представленном случае первой в России симультанной операции в условиях общей комбинированной анестезии у пациентки с синдромом Киндлера оценены критерии трудных дыхательных путей, особое внимание уделено методике выполнения эндотрахеальной интубации трахеи, мониторингу витальных функций организма, соблюдению принципа мультимодальной анальгезии. В связи с высоким риском послеоперационной тошноты и рвоты обоснована необходимость усиления антиэметического эффекта.*

Описание клинического случая. *Основными показаниями к выполнению операции у пациентки в возрасте 49 лет с врождённым буллёзным эпидермолизом (синдром Киндлера) явились жалобы на выраженное затруднение и боль при глотании, снижение аппетита, наличие дисфагии на фоне неравномерного циркулярного сужения пищевода, болезненность при движении глаз, отсутствие носового дыхания на фоне атрезии преддверия носа. Основными задачами оперативного лечения были устранение инвалидизирующих осложнений и улучшение качества жизни пациентки. Многоэтапность в лечении была признана нецелесообразной ввиду необходимости выполнения трёх анестезиологических пособий с высоким риском дополнительных повреждений ротоглотки и верхних дыхательных путей при интубации трахеи, в связи с чем принято решение о симультанном оперативном лечении осложнений основного заболевания. Длительность операции составила 195 минут, анестезии — 210 минут. Выполнено устранение выворота век, рассечение симблефарона, иссечение атрезии преддверия носа и эндоскопическая дилатация стриктуры пищевода. Послеоперационный период протекал благоприятно, отмечено восстановление функции носового дыхания, органов зрения и устранение дисфагии. При обследовании через 11 месяцев после операции признаков рецидива устранённых осложнений основного заболевания не выявлено.* ***Заключение.*** *Повышение безопасности и профилактика ятрогенных осложнений во время проведения анестезии у пациентов с буллёзным эпидермолизом является важнейшей задачей. Развитие современных медицинских технологий с использованием микрохирургических и эндоскопических методик, персонализированного подхода в выборе анестезиологического пособия позволяют более широко использовать симультанные операции в лечении осложнений у пациентов с синдромом Киндлера.*

Ключевые слова: *синдром Киндлера; буллёзный эпидермолиз; трудные дыхательные пути; общая анестезия; дилатация стриктур; эндоскопическая баллонная дилатация.*

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The presence of epidermolysis bullosa in patients classifies them as the individuals with predictable difficult airways, which pre-determines a large number of specific features both when preparing and conducting the surgery, as well as during the post-operative management. Among the main problems of the surgical period that are worth noting, there are difficulties when ventilating by means of a face mask, by direct laryngoscopy and by intubation.

Until the present moment in Russia and worldwide, there were no presented cases of anesthetic management of simultaneous surgeries in adult patients with Kindler syndrome. Our article has demonstrated the first experience of simultaneous surgery in

a patient with congenital epidermolysis bullosa (Kindler syndrome) with an accent to specific features of conducting the combined general anesthesia.

CLINICAL CASE DESCRIPTION

Patient information

Female patient B., aged 49 years, hospitalized to the Burn Department with Plastic Surgery Unit of the Federal State Budgetary Institution "The Nikiforov's Russian Center of Emergency and Radiation Medicine" under the Ministry of the Russian Federation for Civil Defence, Emergencies and Disaster Relief.

The anthropometrical data were the following: body length 156 cm, body weight 47 kg, body mass index 19.31 kg/m^2.

Case history. The patient has the disease from the moment of birth. She was born in a multi-child family, being the outcome of her mother's 10th pregnancy. Twelve months after birth, her skin started having bubbles, both spontaneously and after insignificant injuries. From the age of 5 years she started noting the adhesions in her fingers. From the age of 10 years, besides dizziness, palpitations and increased sweating at the open sun, she started noting gradual worsening of microstomia. According to the data from histological and genetical testing, the Kindler syndrome was confirmed. Pathological mobility of teeth, reported from the age of 16 years, has led to their further painless loss until complete edentia (incapable of wearing the prostheses due to traumatizing the oral cavity mucosa). At the age of 27, there was an episode of grade IV dysphagia with a background of a foreign body in the esophagus: she underwent mediastinotomy with removing the foreign body from the esophagus and with further draining. Due to having a syndactyly in her palms, she was operated at the age of 6, then at 17 and 20 years with grafting the cleaved transplants. At the age of 35 years, upon examination, hydronephrosis was found in the right kidney, in 2021 she underwent stenting of the right urinary duct. From the age of 40, the patient was noting the difficulty of nasal breathing and discomfort in the frontal area caused by narrowing of the nasal passages. In 2020 she underwent the dissection of synechias and the excision of strictures in her left nasal passage. At the present moment, the patient is using silicone dilators for preventing the recurrence. Comparing to the hospitalization in 2021, significant worsening is reported for the condition of the eyes due to the progression of conjunctival adhesions.

The main indication for conducting the surgery was the complaints from the patient of significant difficulties and pain upon swallowing, aggravating in the morning (due to which, only the intake of liquid foods was possible); decreased appetite; presence of grade III–IV dysphagia (Bown scale) with a background of inhomogeneous circular narrowing of the esophagus at the level of the bodies of C7–Th1 vertebral bones with a length of up to 8.6 mm and with the maximal narrowing of the lumen up to 1.6 mm according to the data from esophageal radioscopy; complaints of pain when moving the eyes, lacrymation and eye redness with a background of ectropion, subtotal symblepharon in the lower eyelid fornix, pseudopterygium in both eyes; absence of nasal breathing on the right side with a background of complete atresia of the nasal vestibule on the right side and partial atresia of the nasal vestibule on the left side.

Laboratory and instrumental diagnosis

The physical status of the patient corresponded to class II–III of the scale by the American Society of Anesthesiologists (ASA). The surgical intervention, by its extent and type, was considered as the surgery with moderate traumatic degree. Preoperative evaluation of the status of the upper airways has revealed the risk factors of difficult mask ventilation according to the MMMMASK scale (Mask seal due to the absence of teeth; Mallampati — class IV), difficult installation of the supraglottic air tube according to the RODS scale (R — limited opening of the mouth) and difficult direct laryngoscopy. The criteria for difficult airways were also determined: mouth opening — 2.9 cm (microstomia) (Fig. 1), large tongue, complete edentia, thyromental distance — 6 cm, sternomental distance — 9 cm, hyomental distance — 4.5 cm, Mallampati test — IV (Fig. 2), presence of chronic erosions in the oral cavity (Fig. 3).

Provisional diagnosis

Congenital epidermolysis bullosa, Kindler syndrome. Complete edentia. Microstomia. Chronic erosion of the hard palate. Dysphagia grade III–IV. Esophageal stenosis. Protein-energetic deficiency of moderate degree of severity. Chronic mild degree iron-deficient anemia. Autoimmune thyroiditis, nodular nontoxic goiter, subclinical hypothyroidism. Hypertensive disease stage II. Arterial hypertension grade I. Mild eccentric hypertrophy of the left ventricle. Hydronephrosis of the right kidney, chronic pyelonephritis.

Treatment

The main tasks of surgical treatment were the elimination of incapacitating complications and the improvement of the quality of life for the female patient.

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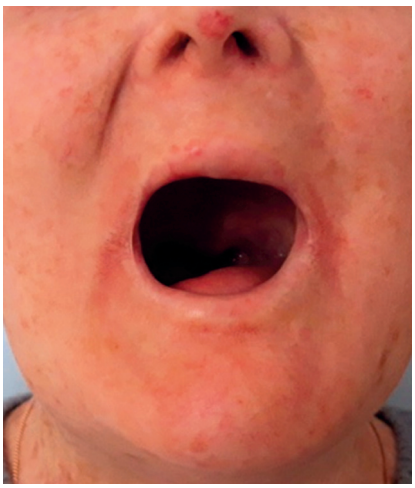

Fig. 1. Cicatricial stricture of the mouth with the formation of microstomia.

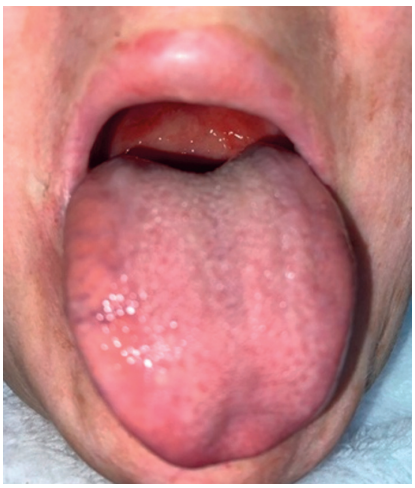

Fig. 2. Class IV oropharynx structure according to S.R. Mallampati.

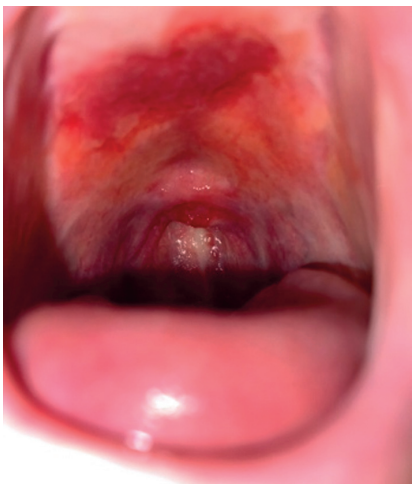

Fig. 3. Chronic erosion of the hard palate.

When planning the surgery, the multiplicity of stages in the treatment was deemed impractical due to the necessity of conducting three anesthetic support procedures with high risk of additional damaging the oropharynx and upper airways upon tracheal intubation. The traditional scales of evaluating the risk of difficult intubation — El-Ganzouri Risk Index, LEMON, Arne, MOSCOW-TD — were also inapplicable due to the absence of the possibility of measuring the distance between the incisors (complete edentia) as one of the important signs of predicting the difficult intubation. Thus, the patient was proposed to undergo simultaneous surgical treatment of complications of the main disease.

At the first stage, a microsurgical technique was used for dissecting the symblepharon with the elimination of pseudopterygium; other procedures included the application of amniotic covering; the external canthotomy in the left and the right eyes; the elimination of the eversion in the lower eyelid with the grafting of the free dermal flap to the left and the right eyes; the second stage included the dissection of the synechias in the nasal cavity on the left side and on the right side, the dilatation of the nasal valve on the left side with an installation of the rhinological splint containing the airway; at third stage, the procedures included the endoscopic balloon dilation of the cicatrical stricture in the upper third of the esophagus under the intra-operative radiology control.

Due to the specific features of the main disease, implementing the standard algorithm for achieving the passability of the upper airways was hampered. The anesthesiology support was conducted based on the general combined anesthesia with tracheal intubation and artificial pulmonary ventilation. As the temporary vascular access, 18G peripheral venous catheter was used, fixated to the skin with the Mepitac (Sweden) soft silicone-based non-adhesive patch. The premedication used included the administration of Dexamethasone at a dosage of 4 mg (calculated as 0.1 mg/kg), Metoclopramide 10 mg (calculated as 0.25 mg/kg). The preoxygenation with 100% oxygen fraction in the inhaled gas mixture (FiO_2) was performed for 3 minutes. The induction of anesthesia was initiated by means of consecutive intravenous injections of Propofol at a dosage of 100 mg (2–2.5 mg/kg), Fentanyl 0.2 mg (3–3.5 μg/kg) and Rocuronium bromide 20 mg (0.6 mg/kg). The anesthesia was maintained by the inhalation of Sevoflurane (minimal alveolar concentration 0.8–1.0%) and by the bolus injection of Fentanyl (1 μg) as needed during the traumatizing stages of surgical treatment. The oxygen fraction in the breathing mixture was 50% with the flow rate of anesthetic gas mixture being 1 l/minute. In order to minimize the injury inflicted to the mucosal membranes when conducting the intubation, water-based lidocaine gel was used — Cathejell (Austria).

For the purpose of preventing the damage of trachea by the cuff of the endotracheal tube, an optimal pressure was maintained in it. In order to conduct the intubation, the endotracheal tube made of Ivory-type soft polyvinyl chloride was used along with the No. 6.5 cuff. The cuff pressure was maintained using the manometry at the level minimally acceptable for hermetization — 20 cmH2O with controls every 15 minutes during the whole course of surgery. If necessary, cuff pressure correction was made.

The intubation of the trachea was done using the videolaryngoscopy method with the C-MAC

laryngoscope (Karl Storz, Germany) and the "D-BLADE" blade. The laryngoscopic findings corresponded to class IIa according to the Fremantle scale of the Cormack–Lehane classification system. The intubation employed the modified bougie method. The fixation of the endotracheal tube was performed using the wraps, protecting the skin with Mepilex (Sweden) silicone-based bandage (Fig. 4). The artificial pulmonary ventilation was done using the Mindray WATO EX-35 anesthesia machine (China) following the mode of pressure control ventilation (PCV).

The monitored vital parameters included the pulse-oximetry, the carbonometry, the electrocardiography (ECG), the non-invasive measurement of blood pressure and thermometry. The blood circulation parameters (blood pressure — non-invasive, heart rate, ECG) were controlled at all the stages of surgical intervention, as well as in 2 hours after surgery at the hospital ward. These parameters had stable values at all the stages. In order to prevent the skin damage when fixating the ECG electrodes and the peripheral venous catheter, the soft silicone-based patches were used (Mepitac, Sweden) (Fig. 5).

Under the cuff of non-invasive blood pressure measurement equipment, the Rolta-soft (Germany) synthetic cotton layer was placed. For preventing the skin damage, under all the areas of bony prominences, gel pads were placed for the whole surgical intervention.

The duration of surgical intervention was 195 minutes, the anesthesia lasted for 210 minutes. In order to observe the multimodal principle of post-operative analgesia, 30 minutes before the end of surgery, followed the intravenous administration of 30 mg Ketorol solution and 1000 mg of Paracetamol. In order to support the antiemetic effect of Dexamethasone and Metoclopramide (control of nausea and vomiting), to the end of surgery, additional administration of Ondansetron was conducted at a dosage of 4 mg (risk of post-operative nausea and vomiting in a patient when applying the Apfel scale is 3 points, or 60%). The extubation was carried out after the complete re-gaining of consciousness and of the neuromuscular conductivity. After 2 hours in a specialized Department ward, additional evaluation of the post-operative nausea was performed with the detailing of the patient's subjective sense of foreign body presence, coughing and difficulties while breathing after removing the endotracheal tube.

The post-operative period had a favorable course without complications. No complaints regarding the status of the upper airways and the oropharynx after the extubation were reported by the female patient. No episodes of post-operative nausea or vomiting were registered at the early post-surgery period. The female patient has noted a significant improvement in her ability to shut the eyelids with a background of complete survival of the transplants in the lower eyelids.

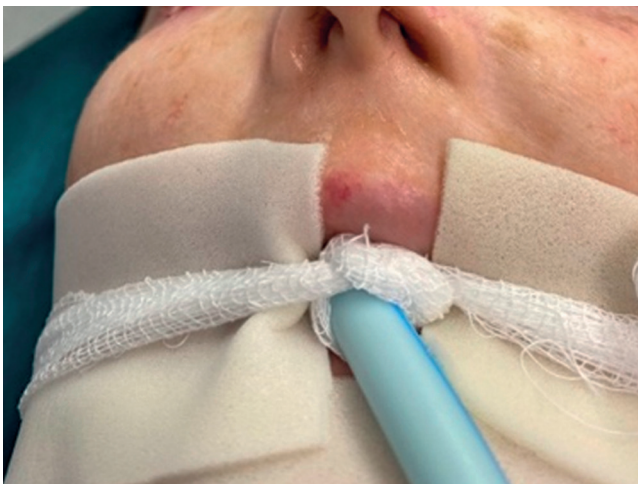

Fig. 4. The method of protecting the skin during the fixation of endotracheal tube using non-adhesive silicone dressings.

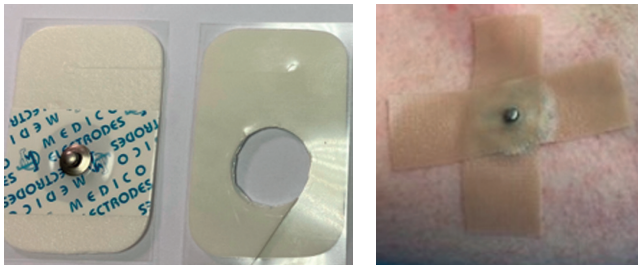

Fig. 5. The method of fixating the electrodes for ECG-monitoring with silicone patches with the adhesive part removed.

Restoring the functions of nasal breathing, of the visual organs and the elimination of dysphagia using the method of endoscopic balloon dilation has allowed for discharging the female patient on day 8 after surgery in generally satisfactory status for further out-patient treatment.

Eleven months after surgery, during the repeated visual examination and general check-up, no signs of recurrence of the eliminated complications of the main disease were detected in the patient.

DISCUSSION

The most frequent non-dermal manifestations of the Kindler syndrome are the damage of the gastrointestinal tract, of the urogenital system and of

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the visual organs. The national and foreign scientific literature has insufficient data on the selection of anesthesia method and on the perioperative managing of this category of patients. Besides, there are no data found on arranging the simultaneous surgeries in the settings of general anesthesia in Kindler syndrome patients in the accessible literature sources. Currently, a certain experience was gathered on selecting the anesthesia in case of surgical treatment among the patients with other types of epidermolysis bullosa, which, generally, depends on the severity of the main disease, as well as on the extent and the duration of surgical intervention. According to the literature data, in patients with epidermolysis bullosa, the methods that can be safely used include the general anesthesia, the neuraxial and the regional types of anesthesia [4]. During the period of preparing the patient for surgery, just like at the stage of its completion, it is important to keep in mind the necessity of preserving the patient's ability for unassisted relocation to the surgery table, due to which the preanesthetic medication in adult patients is generally not used [5].

According to the data from S.L. Solanki et al. [5], general anesthesia is the method of choice in patients with Kindler syndrome. At the same time, we suggest it is important to keep in mind that this type of anesthesia in such patients is associated with traumatic manipulations (direct laryngoscopy, videolaryngoscopy, mask ventilation) and risks of developing large bubbles in the laryngeal part of throat when using the devices intended for assuring the passability of the airways (air lines, endotracheal tubes). According to the opinion from B.Z. Mello et al. [6], when using the lubricants with abundant lubing the laryngoscope blade and the endotracheal tube, the risk of bubble formation significantly decreases.

Taking into consideration that Kindler syndrome patients are related to the category of patients with difficult airways, the conduction of combined general anesthesia with tracheal intubation remains quite a difficult task even for the experienced anesthesiology and resuscitation physicians, also due to the possible necessity of emergency use of surgical methods for restoring the passability of the upper airways (tracheostomy, cricothyrotomy) in case of bubbles forming with the development of asphyxia [7]. The issue of using supraglottic air tubes until the present moment remains disputable, for even the minimal traumatization during this procedure can contribute to the formation of bubbles in the mucosal membrane of the laryngopharynx [7]. Besides, there are insufficient data on selecting the devices and on the practical features of using the supraglottic air tubes in patients with epidermolysis bullosa [4].

Tracheal intubation, as the most reliable method of protecting the upper airways, especially in the presence of dysphagia, from our point of view, is the method of choice when arranging the anesthesia in this category of patients. In cases of single-level lesions in the esophagus, the balloon dilation can be carried out in the settings of intravenous anesthesia, without the tracheal intubation [8], while in cases of multi-level lesions — only in the settings of general anesthesia with the intubation of trachea.

In the presented clinical case, we have demonstrated the successful usage of video-assisted tracheal intubation with the background of microstomia in a Kindler syndrome patient, however, care should be taken regarding the possibilities of successful usage of fiber optic methods in such patients [5]. Sadly, but, according to our own experience of treating the patients with congenital epidermolysis bullosa, as well as according the experience of the foreign colleagues, it is not always possible to perform the endotracheal intubation using fiber optic techniques, for some cases require combining it with videolaryngoscopy [9].

In all the patients with congenital epidermolysis bullosa, regardless of the type of diseases, there are high risks of perioperative complications related to the intra-operative monitoring of vital functions, such as damaging the skin or mucosa when conducting the ECG monitoring, pulse oximetry, non-invasive measurement of blood pressure, providing the temporary vascular access (catheterization of the peripheral and central veins). There is no doubt that the major importance in the work of an anesthesiologist-intensivist managing such patients belongs to the use of medical products based on silicone without the adhesive components, not leading to iatrogenic damage of the skin or mucosal membranes.

CONCLUSION

The presented clinical case demonstrates the possibility of safely performing the simultaneous surgery in patients with congenital epidermolysis bullosa. The issue of the extent of surgical intervention will be defined for each patient on an individual basis. Protecting the skin and the mucosal membranes when arranging the anesthetic support in Kindler syndrome patients is the fundamental principle that allows for avoiding complications.

The development of modern medical technologies with using the microsurgical and endoscopic methods, the usage of personalized approach in selecting the anesthetic support allow for wider application of simultaneous surgeries in the treatment of complications in patients with Kindler syndrome.

ADDITIONAL INFORMATION

Author contributions: *V.I. Kornev*, *V.M. Machs*, *A.S. Pleshkov*, conducting the anesthesia and surgical treatment of the patient; *V.I. Kornev*, *M.V. Nikiforov*, consulting and examining the patient; *V.I. Kornev*, analyzing the treatment results, supervising the treatment and discussing the treatment results, compiling the article text. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The Case of a Patient with Acute Herpes-Associated Retinal Necrosis

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ABSTRACT

BACKGROUND: *Acute retinal necrosis is a serious uveal syndrome of viral origin, which manifests with inflammatory reaction in the vitreous body and in the anterior chamber of the eye, along with the rapidly progressing peripheral necrotic retinitis and occlusive vasculitis. This condition is complicated by retinal detachment in 65–75% of the cases, which may lead to the complete loss of vision. The prognosis for the patients with acute retinal necrosis is generally unfavorable: in case of late diagnostics and insufficient treatment, there is a risk of irreversible blindness, while in 60% of the cases, a decrease in the visual functions below 0.1 is observed.* ***CLINICAL CASE DESCRIPTION:*** *The female patient M., aged 57 years, in 2023 was admitted with the complaints of decreased vision acuity and photophobia in her right eye developing 2 months after a previous episode of acute respiratory viral infection. Physical examination data for the right eye (OD): best corrected visual acuity 0.2, intraocular pressure 29 mm.Hg., the anterior-posterior size is 23.06 mm; according to the biomicroscopy data — pericorneal injection of the conjunctiva and variously sized white-colored precipitates along the whole corneal endothelium. 3 weeks after the initial treatment, the patient had retinal detachment with a decrease in visual acuity to light perception with proper light projection. After the conducted conservative and surgical ophthalmological treatment, including the treatment prescribed by the Infectious Disease Physician, from the beginning of 2024 and to the present day, the periodical control examinations reveal the best corrected visual acuity of 0.1–0.2 in the right eye (OD) of the patient. The intraocular pressure is 15–16 mm.Hg, the anterior-posterior size in 2025 became equal to 21.63 mm. The field of vision has changed insignificantly, without any clear negative changes. Ophthalmoscopically and according to the data from the optical coherence tomography, there is a persisting cystous intraretinal edema, tangential-traction syndrome and pre-retinal membrane in the right eye with no negative changes; the retina is attached in all the meridians.*
CONCLUSION: *This case underlines the importance of the combined and multidisciplinary approach to the diagnostics and treatment of ophthalmological diseases caused by viral infections.*

Keywords: *acute retinal necrosis; herpesviral infections; uveitides; microinvasive vitrectomy; clinical case.*

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BACKGROUND

Acute retinal necrosis (ARN) represents a syndrome of acute panuveitis with retinal periarteritis, which progresses into the diffuse necrotic retinitis and retinal detachment. The syndrome was first described in 1971 by A. Urayama et al. [1]. In 1982, a research conducted by the team of W.W. Culbertson using the electronic microscopy, allowed for detecting the herpes virus in all the layers of the affected retina, which has confirmed the participation of viruses in the development of the disease. The main etiological factors of acute retinal necrosis are the *Varicella zoster* virus, as well as the Herpes simplex virus (HSV-1 and HSV-2), the Cytomegalovirus and the Epstein-Barr virus. Extremely rarely ARN occurs as a result of co-infection with several viruses [2–4]. In the pathogenesis of this disease, a definite role can be played by the carriership of the main histocompatibility complex alleles (human leucocyte antigens, HLA), in particular, DQw7, Bw62 and DR4 [5].

Acute retinal necrosis is a socially significant problem, for it belongs to the group of serious inflammatory diseases of the posterior segment of the eye, accompanied by high rates of incapacitation among the patients. The rate of developing ARN varies from 2% to 7% among all the cases of uveitis [6]. Within the territorial borders of the Russian Federation, among the patients with severe uveitides, receiving therapy within the premises of the ophthalmology in-patient unit, ARN occurs in 8.9% of the cases [7].

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Лечение пациента с острым герпесассоциированным некрозом сетчатки

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АННОТАЦИЯ

Обоснование. *Острый некроз сетчатки (острый ретинальный некроз) является серьёзным увеальным синдромом вирусного происхождения, который проявляется воспалительной реакцией в стекловидном теле и передней камере глаза, а также быстро прогрессирующим периферическим некротическим ретинитом и окклюзивным васкулитом. Это состояние осложняется отслойкой сетчатки в 65–75% случаев, что может привести к полной потере зрения. Прогноз для пациентов с острым ретинальным некрозом в целом неблагоприятный: при поздней диагностике и недостаточном лечении существует риск необратимой слепоты, а в 60% случаев наблюдается снижение зрительных функций ниже 0,1.* ***Описание клинического случая.*** *Пациентка М., 57 лет, в 2023 году обратилась с жалобами на снижение зрения, светобоязнь на правом глазу через 2 месяца после перенесённой острой респираторной вирусной инфекции. Данные осмотра правого глаза (OD): максимально корригированная острота зрения 0,2, внутриглазное давление 29 мм рт.ст., переднезадний размер 23,06 мм; по данным биомикроскопии — перикорнеальная инъекция конъюнктивы, разнокалиберные преципитаты белого цвета по всему эндотелию роговицы. Через 3 недели после первичного обращения у пациентки произошла отслойка сетчатки со снижением остроты зрения до светоощущения с правильной светопроекцией. После проведённого консервативного и оперативного офтальмологического лечения, в том числе лечения, назначенного инфекционистом, в течение 2024 года и по настоящее время при периодических контрольных осмотрах показатели максимально корригированной остроты зрения OD у пациентки составляют 0,1–0,2. Внутриглазное давление 15–16 мм рт.ст., переднезадний размер в 2025 году — 21,63 мм. Поле зрения изменилось незначительно, без явной отрицательной динамики. Офтальмоскопически и по данным оптической когерентной томографии сохраняются кистозный интраретинальный отёк, тангенциально-тракционный синдром, преретинальная мембрана на правом глазу без отрицательной динамики; сетчатка прилежит во всех меридианах.* ***Заключение.*** *Данный случай подчёркивает важность комплексного и мультидисциплинарного подхода к диагностике и лечению офтальмологических заболеваний, вызванных вирусными инфекциями.*

Ключевые слова: *острый некроз сетчатки; герпесвирусные инфекции; увеиты; микроинвазивная витрэктомия; клинический случай.*

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According to the data from scientific literature, ARN is often observed in the individuals without serious somatic diseases, less frequently it can be found among the ones suffering from the immunodepressive diseases or undergoing the immunosuppressive therapy. This disease can develop at any age and it is more commonly seen among men [8].

The diagnosis of ARN is set based on the examination results in accordance with the criteria developed by the American Uveitis Society in 1994. The standard criteria include the following: the presence of retinal necrosis foci in the peripheral areas of the retina, the rapid progression of the disease in the absence of antiviral therapy with concentric spreading along the circumference of the retina to the central area, as well as the development of the occlusive vasculopathy and significant inflammatory reaction in the vitreous body [9, 10]. ARN is characterized by an acute unilateral course, while the bilateral variation is observed in 8.7–33% of the cases [11, 12]. With this, both eyes are not always affected simultaneously: generally, signs of the disease in the

second eyeball were developing within 12–14 weeks from the moment of detecting the disease, however, in 3.4% and 13.6% of the cases, this occurred after 2 and 4 years of follow-up, respectively [11, 13].

The prognosis for ARN is generally unfavorable: in cases of late diagnostics and insufficient treatment, blindness develops in 64% of the cases, with the vision acuity decreasing down to less than 0.1 in 60% of the cases. ARN can be complicated by retinal detachment in 65–75% of the cases, by the ischemic neuropathy of the optic nerve, by the occlusion of the central retinal vein and by the haemophthalmos. Ultimately, the disease leads to retinal atrophy, partial optic nerve atrophy and proliferative vitreoretinopathy [14–16].

The treatment of acute retinal necrosis includes the intensive therapy directed at fighting the viruses, the inflammation and at strengthening the immune system, accompanied by the use of antiaggregants and anticoagulants [6, 17]. In case of occurring peripheral ruptures in the retina, laser coagulation is conducted [6]. Surgical treatment methods for ARN complications, such as retinal detachment and fibrosis of the vitreous body, include the vitrectomy [10, 18, 19].

After an episode of ARN, the patient requires dynamic follow-up, allowing for timely detection of the pathological changes that need urgent treatment.

The article provides an evaluation of the efficiency of the conducted treatment in a patient with acute retinal necrosis, developing after a previous episode of acute respiratory viral infection and after an exacerbation of herpetic infection.

CLINICAL CASE DESCRIPTION

Patient information

Female patient M., aged 57 years, in 2023 has visited the Orenburg affiliated branch of the Federal State Autonomous Institution “National Medical Research Center “The Interdisciplinary Scientific-Technical Complex “S. Fyodorov Eye Microsurgery Federal State Institution” under the Ministry of Health of the Russian Federation (FSAI NMRC ISTC S. Fyodorov Eye Microsurgery Federal State Institution under the Ministry of Health of the Russian Federation) with the complaints of decreased vision acuity, photophobia in her right eye developing 2 months after a previous episode of acute respiratory viral infection (ARVI).

Case history. The female patient had an ARVI within a week, after which she was noting the exacerbation of herpetic infection, as well as the development of iridocyclitis in her right eye. No specific treatment for ARVI or herpetic infection was provided to her. Due to the iridocyclitis in the right eye, she was receiving instillations of antibiotics, antiviral medicines, non-steroid anti-inflammatory medications and subconjunctival injections of dexamethasone. With a background of therapy, no clear positive changes were reported and in 2 months after an ARVI, the female patient has noted a rapid deterioration of the vision in her right eye. For the verification of diagnosis, the patient was referred to the Orenburg affiliated branch of the FSAI NMRC ISTC S. Fyodorov Eye Microsurgery Federal State Institution under the Ministry of Health of the Russian Federation.

Of all the concomitant diseases, the patient reports chronic viral hepatitis C and chronic herpesviral infection.

Ophthalmology history — not compromised.

Laboratory and instrumental diagnosis

After an examination, the best corrected visual acuity (BCVA) in the right eye (oculus dexter, OD) was 0.2, while in the left one (oculus sinister, OS) — 0.9–1.0; the pneumotonometry values were 29 and 23 mm.Hg.; the anterior-posterior dimensions of the eyes according to the data from optic biometry were 23.06 mm and 22.9 mm, respectively. The data from the kinetic spheroperimetry are provided in Fig. 1.

According to the biomicroscopy data, the anterior and posterior segments of the left eye were unremarkable. The right eye was showing pericorneal injection of the conjunctiva, variously sized white-colored precipitates all along the retinal endothelium.

Fundoscopy (ophthalmoscopy): the vitreous body of the right eye contains a suspension of fibrin and coagulated blood; the retina is not accessible for examination.

Ultrasound examination using the Quantel Medical Aviso V:5.0.0 (France) ophthalmology diagnostics scanner: the vitreous body of the right eye contains multiple inclusions visualized as bodies, flakes, chords and adhesions, with the retrovitreal areas of turbidity with various echogenicity, non-fixated posterior detachment of the vitreous body (Fig. 2).

Provisional diagnosis

Vitreous opacity, vitreitis, consequences of past iridocyclitis in the right eye.

The recommendations included conducting the endovitreal intervention.

Upon performing the microinvasive vitrectomy with endo-laser coagulation of the retina, the findings include

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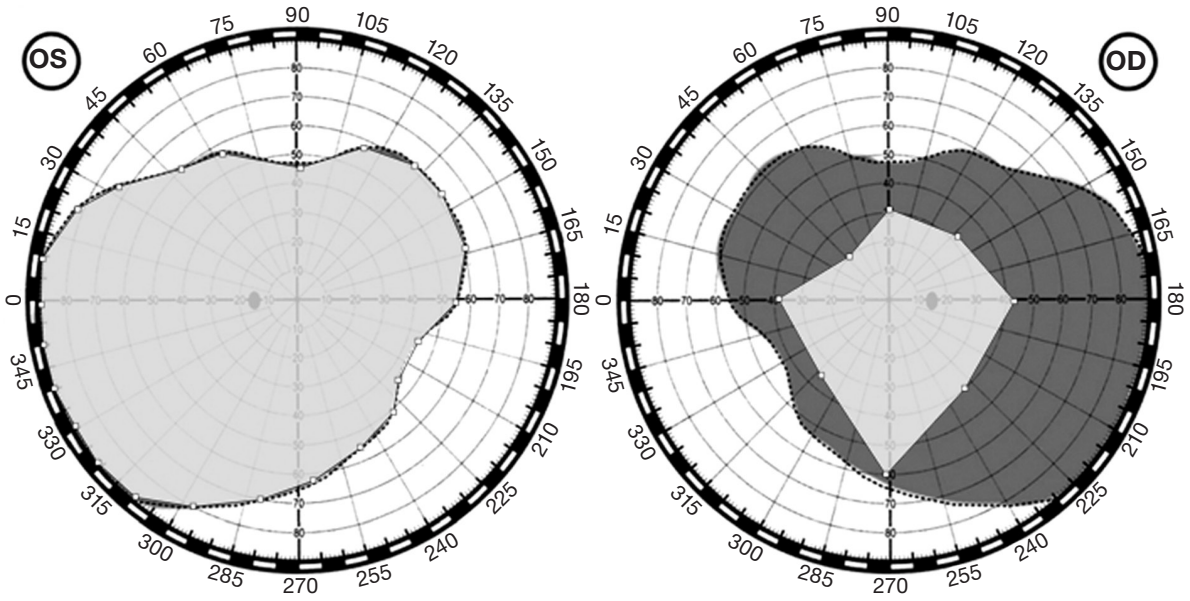

Fig. 1. The kinetic spheroperimetry upon the initial examination: the detected findings include a narrowing of the vision field margins in the right eye (OD), more in the temporal and the nasal meridians, the left eye (OS) is unremarkable.

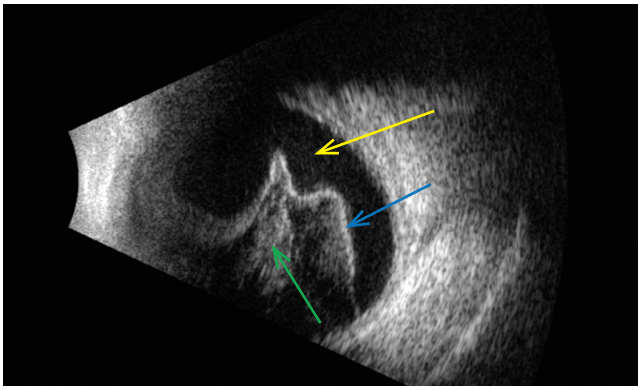

Fig. 2. Ultrasound examination of the right eye: multiple inclusions were found, visualized as bodies, flakes (yellow arrow), strands and adhesions of various echogenicity (green arrow), non-fixated posterior detachment of the vitreous body (blue arrow).

the desolation in the blood vessels of the lower-temporal arcade, hemorrhages and microaneurisms in the nasal meridians at the close and middle peripheral areas of the ocular fundus, where the surgical intervention was actually conducted (Fig. 3).

On the next day after surgery, the female patient was discharged with positive changes for further out-patient treatment with the recommendation to undergo an examination at the infectiologist's office. On discharge, the BCVA of her right eye was 0.75; pneumotonometry — 11 mm.Hg.; the vision field, according to the data from kinetic spheroperimetry, has increased (Fig. 4).

Two weeks after surgery, the female patient has again presented to the Orenburg affiliated branch of the FSAI NMRC ISTC S. Fyodorov Eye Microsurgery Federal State Institution under the Ministry of Health of the Russian Federation with the complaints of rapid deterioration of vision in the right eye, with developing the "curtain" in front of it. During this period, the female patient was examined at place of residence by the infectiologist and was tested for the

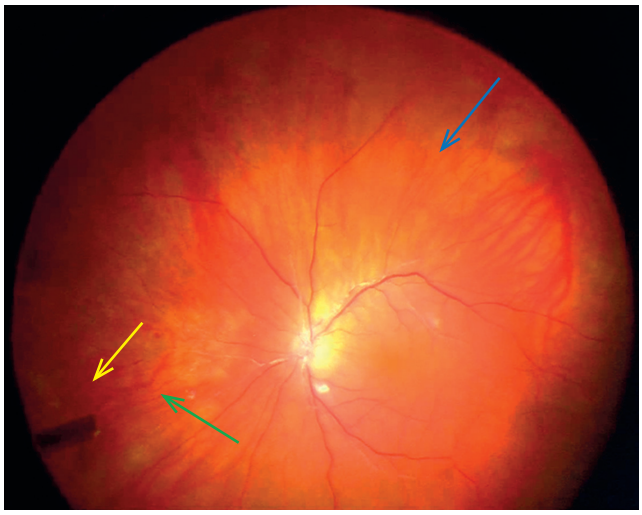

Fig. 3. Intraoperative photography image of the ocular fundus of the right eye: desolation of the vessels in the lower-temporal arcade (blue arrow), hemorrhages (yellow arrow) and microaneurisms (green arrow) in the nasal meridians in the close and the middle periphery of the ocular fundus.

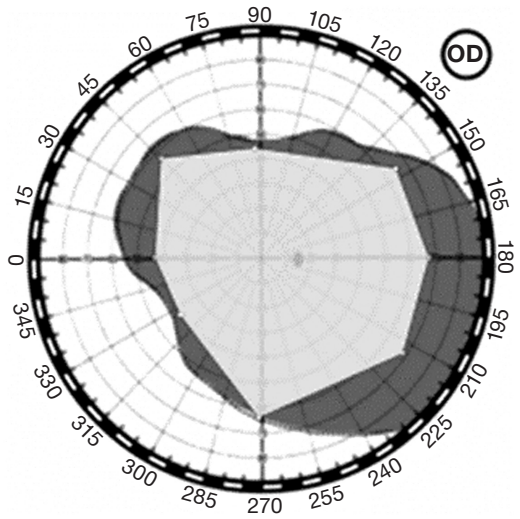

Fig. 4. Kinetic spheroperimetry of the right eye during the first 24 hours after surgery: the observations include significant enlargement of the vision field margins in the right eye.

presence of infections, caused by the *Herpesviridae* family of viruses: an increased titer of antibodies to HSV-1 was found, due to which, by the prescription from the physician, she was receiving glucocorticoids (Prednisolone) at high dosages.

Upon the examination, the BCVA in the right eye is 1/∞ pr.l.certae (light perception with correct light projection), in the left one — 1.0. The pneumotonometry parameters were 16 and 19 mm.Hg., respectively. Due to the absence of spatial vision on the right eye, the field of vision in it was not examined, in the left eye it was normal.

According to the data from biomicroscopy, the anterior and the posterior segments of her left eye were unremarkable. The right eye was showing superficial conjunctival injection, initial turbidity in the eye lens. Fundoscopy (ophthalmoscopy): mobile dome with total retinal detachment and with the rupture from the ora serrata at 5–9 o'clock (Fig. 5, *a*); in the lower- and upper-inner quadrants, as well as in the upper-external quadrant, there is a peripheral necrosis of retina along the ora serrata (Fig. 5, *b–d*).

Ultrasound examination of the right eye: the scanned findings in the vitreal cavity were showing multiple inclusions visualized as bodies and strands; the total retinal detachment was observed in all the meridians at the close, the middle and the marginal periphery with retinal dialysis from the ora serrata at the 5–9 o'clock meridian, the detachment height is up to 8 mm, the retina is mobile (Fig. 6).

Definitive diagnosis

Retinal detachment with retinal tear, acute retinal necrosis (presumably, herpes-associated), avitria, operated haemophthalmos, primary complicated cataract in the right eye.

Treatment

An endovitreal intervention was conducted (retinotomy, membrane peel and tamponade with perfluoroorganic compounds) with simultaneous phacoemulsification of the cataract and an implantation of the intraocular lens into the right eye with further (in 5 days) replacement of the perfluoroorganic compound with silicone oil (Densiron) and retinal endo-laser coagulation.

follow-up and outcomes

On discharge, the BCVA in the right eye was 0.3; the pneumotonometry result was 16 mm.Hg.; the field of vision, according to the data from kinetic spheroperimetry, has increased (Fig. 7).

Fundoscopy (ophthalmoscopy): the vitreal cavity contains silicone oil; the optic nerve disc is slightly pale, monotonous; the retina is attached, the retinotomy margins are adapted, pronounced coagulates were found.

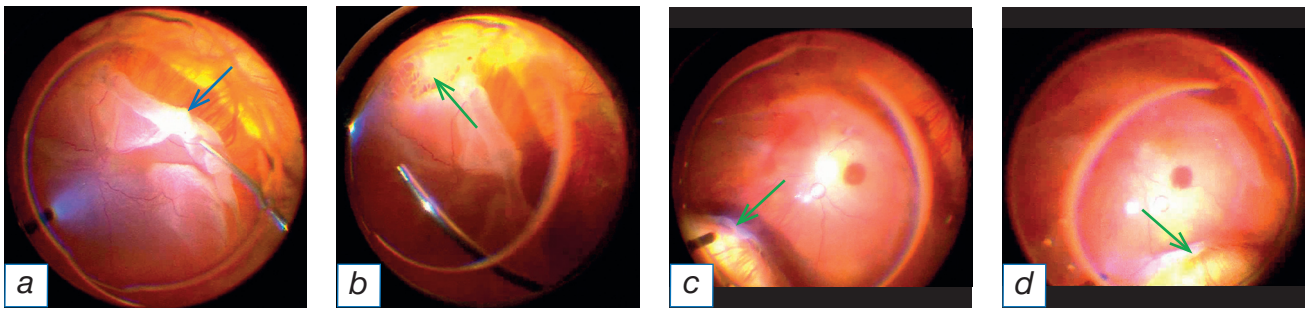

Fig. 5. Intraoperative (2 weeks after surgical intervention) photography images of the posterior segment of the right eye: *a* — total retinal detachment with a tear at 5–9 o'clock from the ora serrata (blue arrow); peripheral necrosis of the retina along the ora serrata (green arrow): *b* — lower-internal quadrant; *c* — upper-internal quadrant; *d* — upper-external quadrant.

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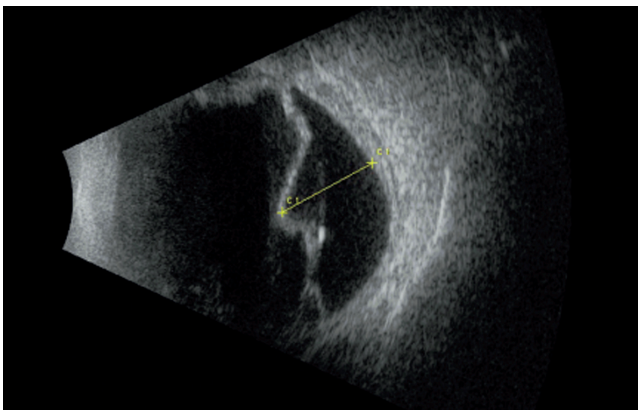

Fig. 6. Ultrasound examination of the right eye 2 weeks after surgery: total retinal detachment is observed in all the meridians at the close, the middle and the marginal periphery with a retinal tear from the ora serrata at the 5–9 o'clock meridian, with a height of up to 8 mm, the retina is mobile.

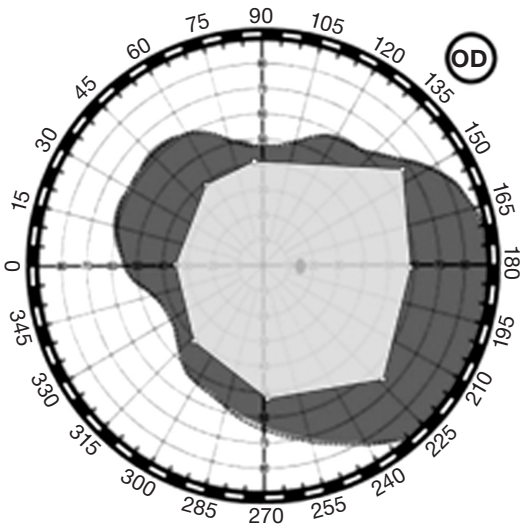

Fig. 7. Kinetic spheroperimetry of the right eye after a repeated surgical intervention: the observations include significant enlargement of the vision field comparing to preoperative (not defined).

During the control examination in 2.5 month after surgery: BCVA in the right eye — 0.35; pneumotonometry — 24 mm.Hg.; the field of vision has practically not changed comparing to the previous examination; the left eye has no changes.

Biomicroscopy of the right eye: superficial injection of the conjunctiva; the intraocular lens is centered. Ophthalmoscopy of the right eye: tamponade with silicone oil, the silicone oil is emulsified; the optic nerve disc is slightly pale, monotonous; the retina is attached in all the meridians; the retinotomy margins are adapted, the coagulated areas are pronounced.

Biomicroscopy and ophthalmoscopy of the left eye — no abnormalities.

A decision was drawn on changing the silicone oil due to its emulsification.

On discharge, the BCVA in the right eye was 0.02; pneumotonometry was showing 10 mm.Hg.; the field of vision, according to the data from kinetic spheroperimetry, has not changed.

Fundoscopy (ophthalmoscopy): the vitreal cavity contains silicone oil; the optic nerve disc is slightly pale, monotonous; the retina is attached, the retinotomy margins are adapted, the coagulates are pronounced.

At the control visit in 4 months after the repeated endovitreal intervention: the BCVA in the right eye is 0.05, in the left eye one — 0.9; tonometry (Maklakov, 10 g weight) — 15 and 20 mm.Hg. respectively. According to the data from kinetic spheroperimetry, a concentric narrowing was found in the margins of the vision fields of the right eye; the left eye shows no changes (Fig. 8).

Biomicroscopy of the right eye: superficial conjunctival injection; the intraocular lens is centered. Ophthalmoscopy of the right eye using the Mirante (Japan) scanning laser ophthalmoscope: tamponade with silicone oil; the optic nerve disc is slightly pale, monotonous; the fovea has signs of cystoid macular edema; the retina is attached in all the meridians, the retinotomy margins are adapted, the coagulates are pronounced (Fig. 9).

The biomicroscopy and ophthalmoscopy findings in the left eye were showing no signs of abnormalities.

According to the data from the optical coherence tomography (RTVue-100, Optovue, USA) a rough impairment of the retinal architectonics was found, along with cystoid intraretinal edema, tangential traction syndrome and a pre-retinal membrane (Fig. 10).

After the conducted conservative and operative ophthalmology treatment, as well as after the treatment prescribed by the Infectious Disease Physician, the patient, from the beginning of 2024 and to the present day, during the periodical control check-ups, has her BCVA values in the right eye varying within the range of 0.1–0.2, the intraocular pressure measured using the Maklakov's method (10 g weight) was 15–16 mm.Hg.; the anterior-posterior dimension of the right eye, according to the data from optic biometry, in 2025 was 21.63 mm. The field of vision in the right eye has changed insignificantly with no clear negative changes. Ophthalmoscopically and according to the data from the optical coherence tomography, there is a persisting cystoid intraretinal edema, tangential traction syndrome;

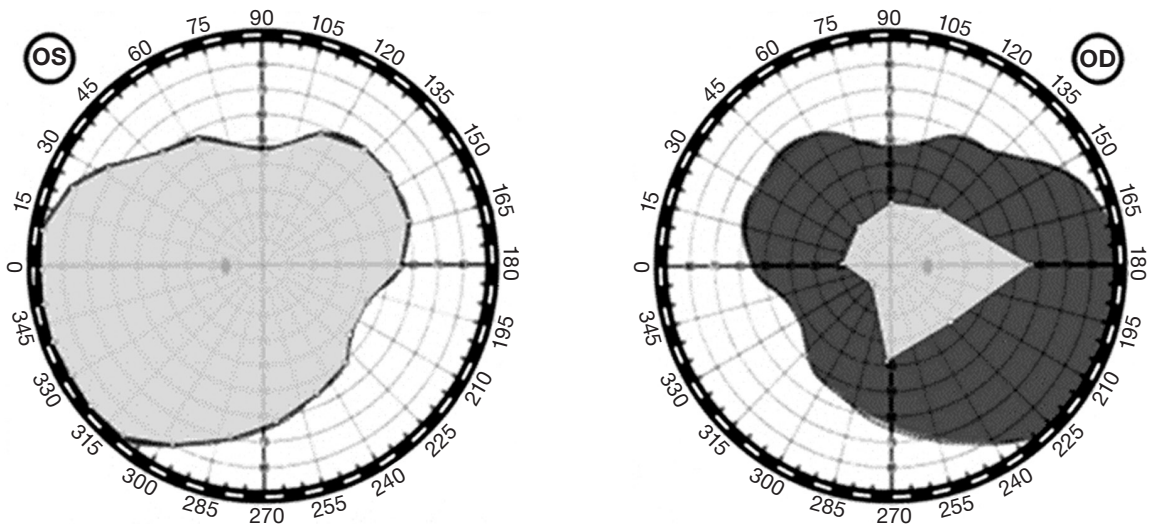

Fig. 8. Kinetic spheroperimetry during the control visual examination in 4 months: concentric narrowing of the vision field margins in the right eye (OD); left eye (OS) — no changes.

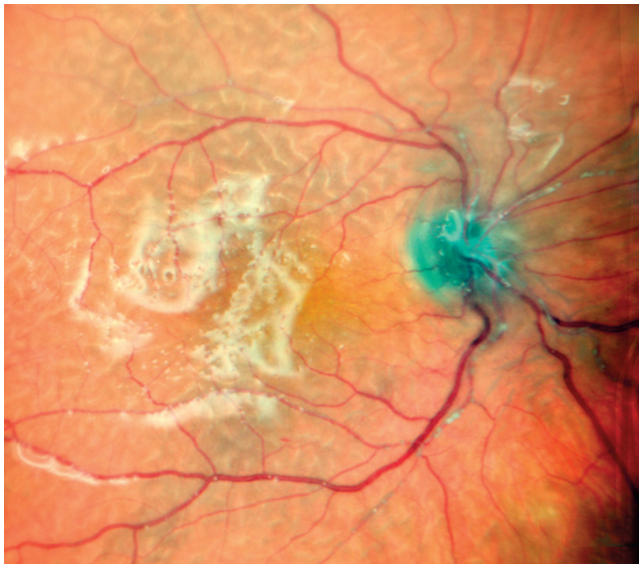

Fig. 9. Photography image of the ocular fundus in the right eye in 4 months: tamponade with silicone oil, the optic nerve disk is slightly pale, monotonous, the fovea has signs of cystoid macular edema, the retina is attached at all the meridians, the retinotomy margins are adapted, pronounced coagulates were found.

the pre-retinal membrane in the right eye has no negative changes; the retina is attached in all the meridians. The left eye shows no signs of abnormalities.

Prognosis

Taking into consideration the pattern of retinal damage, the prognosis regarding the vision is unfavorable. The female patient is still under dynamic medical supervision and continues receiving therapy prescribed by the infectiologist and by the immunologist.

DISCUSSION

This case illustrates the complexity of clinical signs and of managing the patients with ARN caused by the herpesviral infections, with an accent at the necessity for combined approach in the diagnostics and treatment of this disease. It should be noted that the viruses of the *Herpesviridae* family can cause serious eye diseases, including the vitreitis and the acute retinal necrosis, which may lead to the retinal detachment. In the investigated clinical case, despite the adequate treatment, the disease continued progressing, which emphasizes the necessity for a more active approach to the treatment and the importance of thorough monitoring the eye status in patients with such complications.

The examination results indicate that, even after a surgical intervention, the restoration of vision could be insufficient, which requires further research and, probably, implementing new treatment methods. Also required is the development of procedures for timely diagnostics of ARN in patients with herpesviral infections, as well as arranging additional research for the purpose identifying the optimal strategies for therapy and prevention of ophthalmology complications in such patients for improving the disease prognosis and the quality of life.

CONCLUSION

The presented case of the patient with acute retinal necrosis, developing after an ARVI and after an exacerbation of the herpesviral infection, underlines the importance of early diagnostics and combined treatment of viral infections, as well as the necessity

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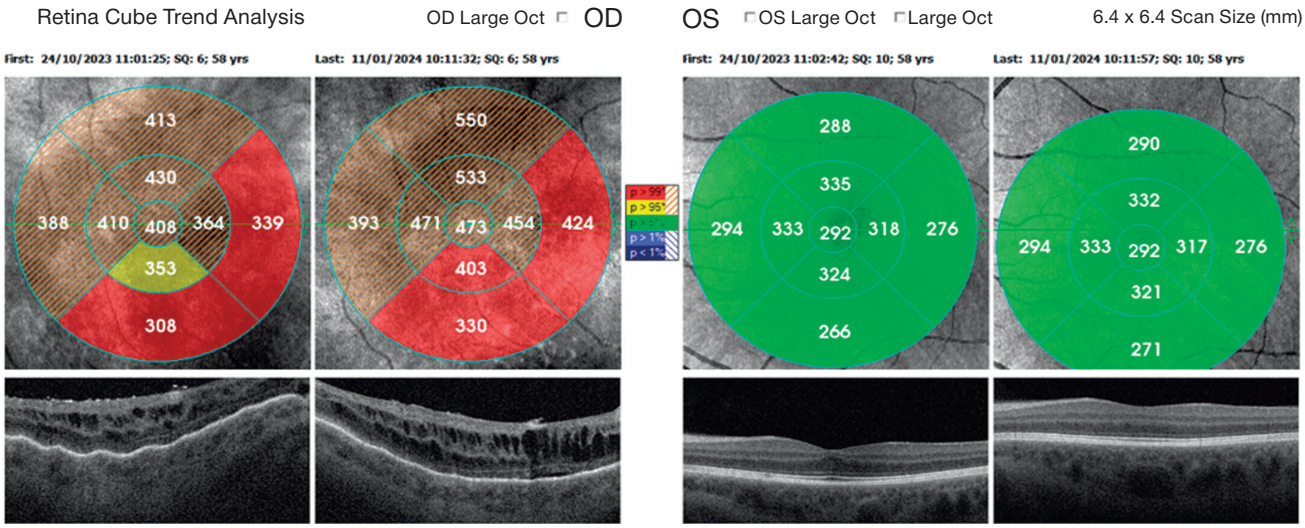

Fig. 10. Optical coherence tomography: rough impairment of the retinal architectonics, cystoid intraretinal edema, tangential traction syndrome, pre-retinal membrane in the right eye (OD); left eye (OS) — unremarkable.

of multidisciplinary approach in the treatment of such diseases. Despite the conducted therapeutic and surgical procedures, the complete restoration of the visual functions in our patient did not occur, due to which, further research is required on the issues of improving the methods of early diagnostics, therapy and prevention of the recurrences of this incapacitating disease, the methods capable of resulting in positive clinical outcomes in patients with ophthalmological complications caused by viral infections.

ADDITIONAL INFORMATION

Author contributions: *A.D. Chuprov*, concept and design of the study; *A.S. Firsov*, surgical treatment and examination of the patient; *D.A. Barinov*, processing of the study results, writing the text of the article. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication: The authors received written informed voluntary consent from the patient to publish personal data, including photographs (with the face covered), in a scientific journal, including its electronic version (signed on 2023 Mar 09). The volume of published data was agreed upon with the patient.

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