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ORIGINAL ARTICLE
Reconstructive

First Russian Experience of Composite Facial Tissue Allotransplantation

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Abstract: The facial allotransplantation technique was first introduced to the general public in 2005. The definition of the face as a complex system of organs that perform social functions made possible the adaptation of this operation into clinical practice. The year 2010 was the starting point for initial research in the Russian Federation. Based on previous achievements and existing world experience in this field, facial allotransplantation was used for the first time in 2015 in St. Petersburg. The goal of this operation was to reconstruct a soldier's central facial area after an electric burn; he was injured in the military line of duty. This article describes complications faced regarding the preparation for this operation, the issues encountered for facial tissue removal, as well as donor selection criteria. Each stage of the composite facial allotransplantation, complications that can occur during operation, milestone results, as well as the subsequent rehabilitation and immunosuppressive therapy during the 4-year patient observation period following surgery, including the description of a single episode of cell-humoral rejection of transplanted tissue, are described in detail. The experience gained from the first facial allotransplantation performed in Russia shows the possibility of using a new composite allograft to correct deformities in the central area of the face with the achievement of a successfully functioning and aesthetically pleasing result after the operation. After 4 years of dynamic observation and individual rehabilitation programs, the main goal of the facial transplantation, that is, social re-adaptation of the patient, was achieved. *(Plast Reconstr Surg Glob Open 2019;7:e2521; doi: 10.1097/GOX.0000000000002521; Published online 25 November 2019.)*

INTRODUCTION

Facial allotransplantation is an experimental procedure and is now at the stage of accumulation and systematization of acquired knowledge on it. The first successful partial facial transplantation was performed by Doubernard in France in 2005. Facial allotransplantations have been performed in the United States since 2009, where a procedure involving the largest volume of transplanted tissues was performed in 2015.[1,2] Currently, global experience includes almost 40 successful allotransplantations,[3] both full and partial; the 32nd surgery, according to the registry, was carried out by the authors in St. Petersburg in Russia in May 2015.

Most authors describe the face as a separate area or structure consisting of different zones, each of which has its own characteristics.[4] Siemionow[5] introduced a concept of the "face as an organ," which allowed for amendment of the legal regulations. In our view, the face is made up of a variety of tissues performing as a whole to fulfill a social function. The social function of the face is crucial, which is why recipients' resocialization after the face transplantation is the main indicator of success and the essence of the whole operation.

MATERIALS AND METHODS

Patient E, a 19-year-old man, was admitted to hospital for treatment of third- to fourth-degree electrical burns to 17% of the surface of the head, neck, and right upper and lower limbs. He was injured on August 09, 2012, in the line of duty while performing military service. Over the period of 3 years, he received >30 reconstructive surgeries, which were performed with the aim of closing the defects, as well

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Received for publication January 15, 2019; accepted September 11, 2019.

DOI: 10.1097/GOX.0000000000002521

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

as to restore vision, and regain functioning of the affected limbs. However, the results of treatment were not sufficient to allow the patient to achieve social adaptation and did not eliminate the major self-identification disorder which he developed after the facial injury. This caused him to attempt suicide on 2 occasions. All possibilities for plastic reconstructive surgery were exhausted, and in view of deficiency of the covering tissues, it was decided to perform allotransplantation of a complex face tissue allograft for patient E.

It is important to note that after the traditional surgical treatment, functional disorders of the damaged right half of the face were insignificant. The main and most difficult target of the reconstruction was the central zone of the face (Fig. 1).

During preparation of the potential recipient for face allotransplantation, informed consent was obtained for the surgery. The patient was fully examined according to the international pretransplantation protocol.

For the purposes of detailed assessment of the damage, the patient underwent several series of 3-dimensional (3D) laser scans of the face, followed by printing out the areas of defect using a 3D printer. This allowed us to carry out more accurate modeling and anatomical positioning of the allograft, both during preparation for the surgery and during the procedure itself (Figs. 2 and 3).

Stages of Preparation for the Face Allotransplantation

Experimental Stage

In preparation for the face allotransplantation in Russia, the authors completed all stages of the world protocol: legal groundwork for the process, and experimental and anatomical studies.

In the period from 2010 to 2014, >40 experimental allotransplantations were performed, followed by cyclosporine monotherapy. Study of the immune response was carried out using a method of quantitative determination of the following subpopulations of lymphocytes: $CD3^+$, $CD4^+$, $CD8a^+$, $CD161^+$, $CD25^+$, $CD45RA^+$, and CD 20^+.[7]

One of the conclusions made during allotransplantation of a revascularized fascial composite allograft, was that we had ascertained the most immunologically beneficial model. A low load on the recipient's immune system was identified when the volume of transplanted tissues was not >25% of the surface of the face and neck, compared with hemifacial and full transplantations. In this group of animals, there were no fatal cases, and the follow-up period was 200 days.[8] The experimental data obtained were taken into account while planning the surgery.

Anatomical Stage

Simultaneously with the experimental research, studies were carried out on unfixed cadaveric material for understanding the anatomical features and practicing technical aspects of withdrawal of a face tissue complex from the donor. The work was performed on 46 cadaver models, during which both a full-face model and partial face allografts were considered.

It should be noted, however, that nearly every tissue complex model is unique, especially when planning partial facial allotransplantation. The criteria for an ideal tissue complex model were as follows: low minimum immunological load, complete restoration of lost functions of the face, and the most aesthetically beneficial result for the patient.

Most favorable in all 3 of these aspects was a model of allotissues that was designed specifically for this surgery. This included the anterior wall of the frontal sinuses; soft tissues of the forehead, including the frontal muscle; fasciae, subcutaneous fat; skin; whole nose, including bone tissue, nasal cartilages; mucosa; muscles; and part of the

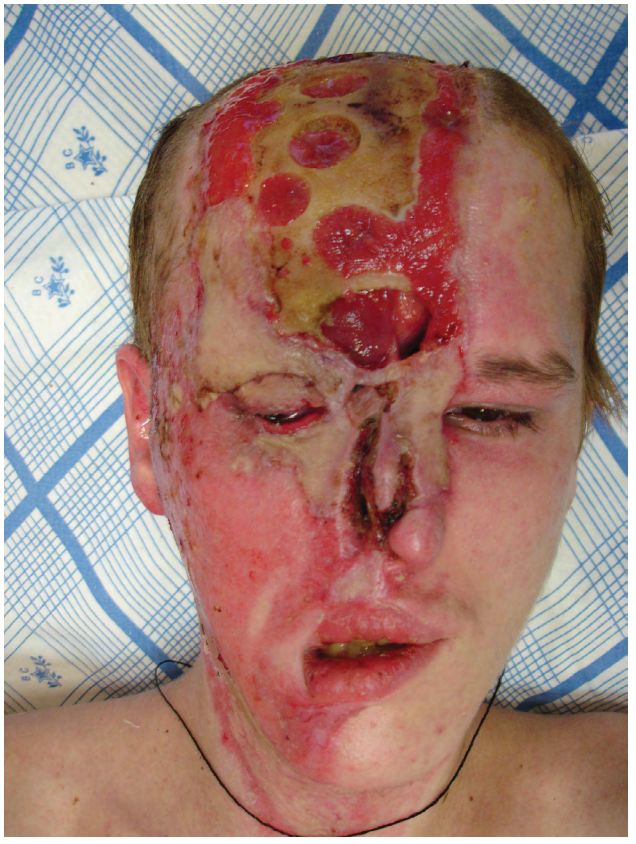

Fig. 1. Appearance of patient E, after the completion of traditional rehabilitation treatment and before facial allotransplantation.

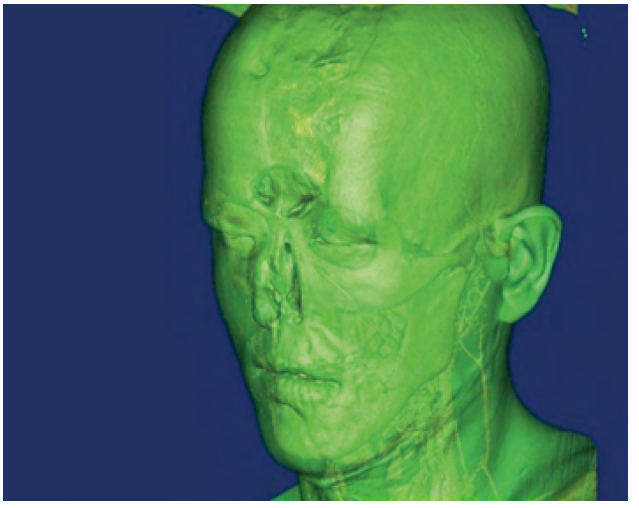

Fig. 2. Scan of the patient's face during the preparations for allotransplantation surgery.

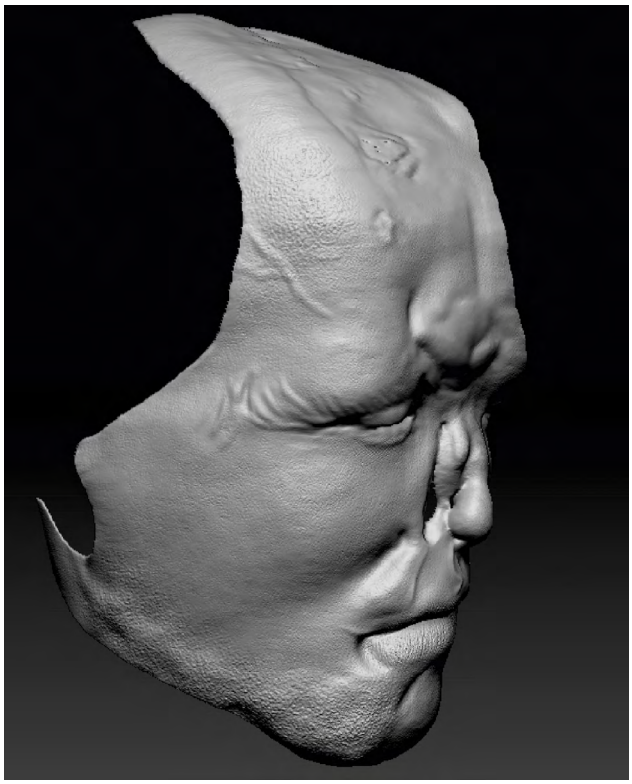

Fig. 3. Three-dimensional print of the surface of patient E's facial deformity.

soft tissues of the midface with 2 facial arteries and facial veins (Fig. 4).

Donor Stage

The donor matched the defined criteria developed for a potential facial tissue donor: an identified person, diagnosed brain death, age 18–55 years, preferably male sex, no damage of the facial skeleton, no skin diseases, no inflammatory processes in the area of operation and in the ENT organs, no atherosclerosis of external and common carotid arteries, artificial ventilation for not >96 hours, stable hemodynamics, and a match with the recipient's anthropometric data.

Immunological examination of the recipient and the donor included assessment of blood group, degree of immunological sensitization of the recipient, recipient's phenotype, donor's phenotype, and a cross-match test. The donor was also examined for markers of infectious diseases (human immunodeficiency virus, syphilis, hepatitis B and C, and cytomegalovirus).

Information about the presence of potential donors in medical organizations from 28 regions of the Russian Federation was collected by the Organ Donation Coordination Center. The search for a suitable donor took 9 months.

In May 2015, the Coordination Center received information about a potential male donor of 51 years of age with a traumatic brain injury and started the procedure for ascertaining brain death. Laboratory, instrumental and immunological studies determined compatibility with the recipient.

After the pronouncement of brain death, intensive therapy of the donor continued, aimed at prevention of purulent-septic complications, correction of water and electrolyte balance, hypotension, hyperglycemia, polyuria, and hypothermia. Consent was obtained from the relatives of the deceased to explant facial tissues.

The facial allotransplantation algorithm was divided into 3 consecutive stages, with repeated training in the operating theater using cadaveric material.

Stage 1. Explantation of the Facial Tissue Complex and Closure of the Defect with a Death Mask

The allograft explantation was performed according to the "full-face" model, with involvement of the facial artery and vein. After complete dissection of the facial allograft, the mucous membrane of the ethmoid sinus and external wall of the frontal sinuses were removed, and the external carotid artery was cannulated, followed by conservation with Custodiol HTK Solution (Essential Pharmaceuticals, LLC) cooled to 2°C. Perfusion efficiency was determined by the change in the color of the graft and the outflow of

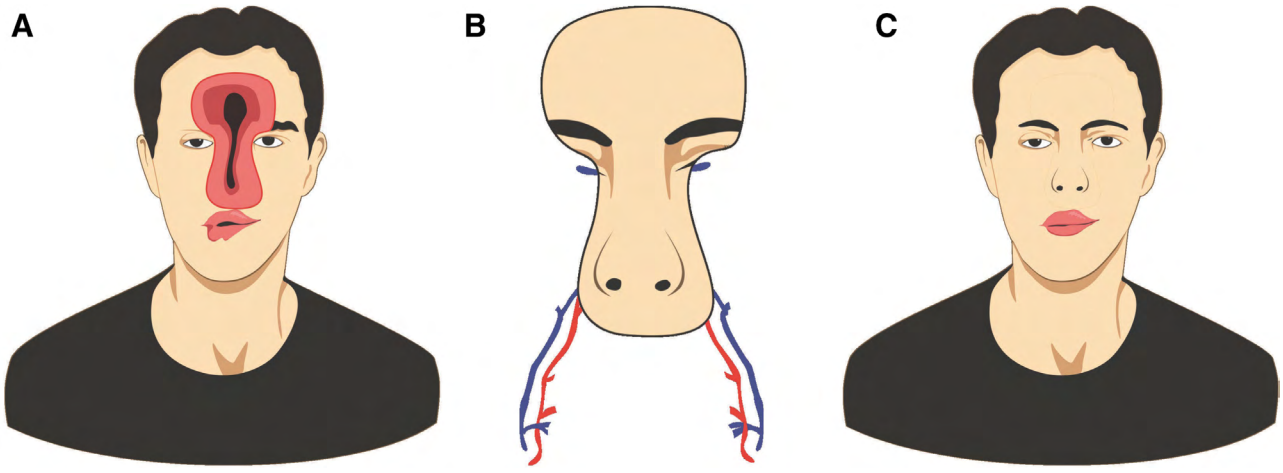

Fig. 4. Models of the different stages of partial face allotransplantation. A, A model of the patient's face. B, A model of the composite allotissues. C, Planned results of the operation.

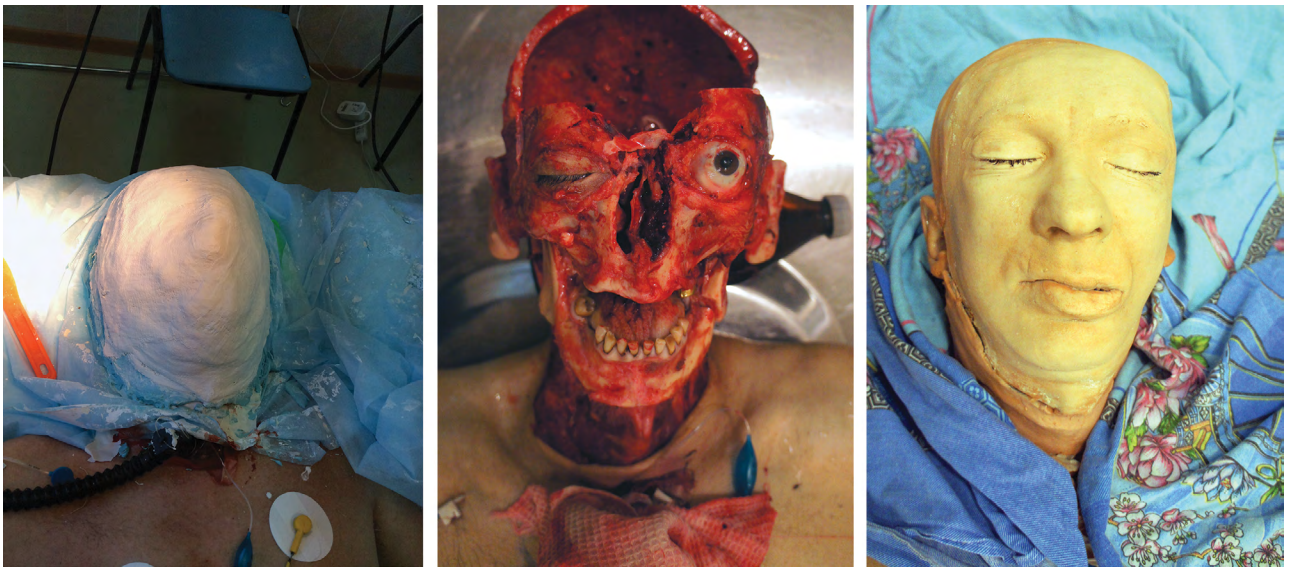

Fig. 5. Manufacturing stages of the donor's death mask.

the solution through the venous system. Duration of the explantation was 7 hours 15 minutes.

In our opinion, explantation of full-face tissues made it possible for us to have a reserve of plastic material, to perform effective perfusion and preservation of the tissues, and to train on the "full-face" explantation technique in real conditions.

According to the principles of humane treatment of the body of a deceased person, the donor's facial tissue defect was closed with a death mask (Fig. 5). At the final stage of manufacturing the death mask, the finished silicone model of the face was cleaned of artifacts, eyebrows and eyelashes were fixed, and makeup was applied. Preparation of the mask took about 8 hours.

Stage 2. Preparation of the Recipient

Preparation of the recipient bed consisted of removing granulating tissues from the cavity of the frontal sinuses, excision of affected tissues in the upper and middle zone of the face within the defect area, and isolation of the external jugular vein and external carotid artery on the right and on the left.

Stage 3. Allotransplantation of the Facial Tissue Complex

This surgical stage included the following tasks: modeling, inclusion of the allograft into the bloodstream, and adaptation of its bone and soft-tissue complex of tissues in the donor-recipient system.

Inclusion of the allograft into the bloodstream was by means of end-to-side anastomosis of the recipient's external carotid artery with the donor's facial artery on the right, and of the recipient's external jugular vein with the donor's facial vein on the left. Standard methods were used to check the competence of the anastomoses and to obtain a sufficient capillary response from donor tissues, including at distal level (Figs. 6 and 7).

The osteoplastic stage included tamponade of the frontal sinuses with a free-muscle autograft (Fig. 8), anatomical positioning of bone and soft-tissue structures of the allograft, and their fixation to the recipient bed with miniplates (Figs. 9–11).

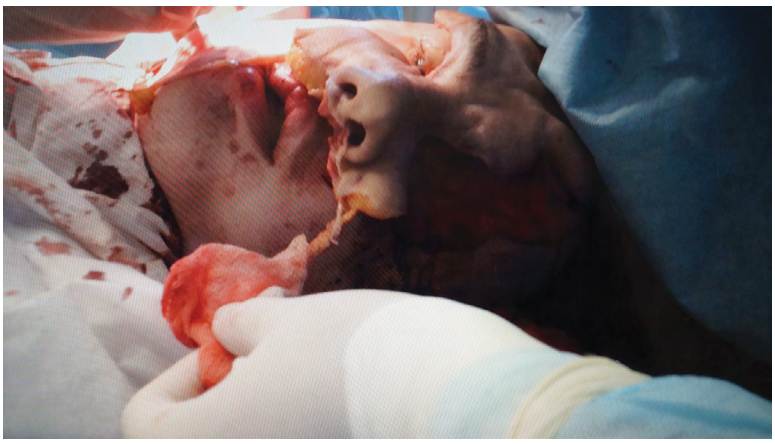

Fig. 6. Integration stage of the donor's allograft to cover the facial deformity of the recipient.

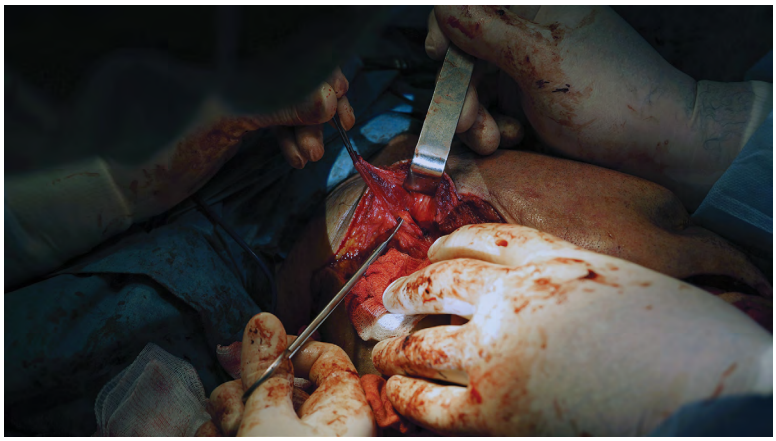

Fig. 7. Microsurgical stage showing arterial and venous anastomoses.

During the surgery, the recipient underwent allotransplantation of a "signal" Chinese flap in the lower third of the left forearm, to obtain biological material for step-by-step biopsies for histological and immunohistochemical studies throughout the lifetime of the donor tissues (Fig. 12).

Immunological Protocol

The immunosuppressive therapy protocol was divided into initial and supporting stages. In accordance with the adopted protocol, a control biopsy of the skin signal flap was performed on days 3, 7, 14, 21, and 30, and every month after that (Fig. 13).

The following complications were observed after the face allotransplantation: disseminated intravascular coagulation syndrome, acute respiratory distress syndrome, moderate posthemorrhagic iron-deficiency anemia, moderate thrombocytopenia, systemic inflammatory reaction syndrome, and false aneurysm of the facial artery on the right. Standard infusion-transfusion, respiratory, and antibacterial therapy was administered, supplemented with hemodiafiltration as needed. This allowed us to eliminate the fluid overload, which was inevitable after a 16-hour intervention. Analgosedation was performed using dexmedetomidine, which at stable hemodynamics allowed us to give the recipient the required level of sleep and pain relief.

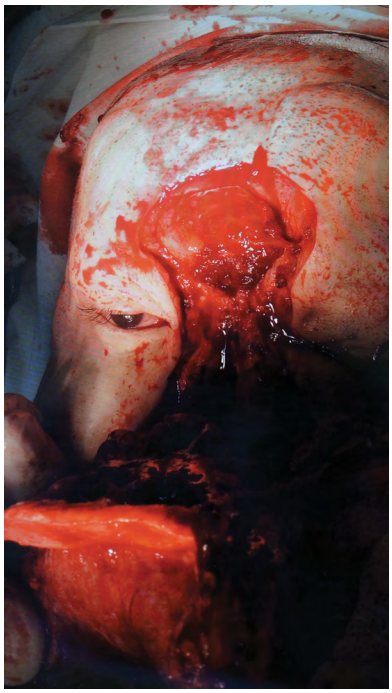

Fig. 8. Tamponade of the patient's frontal sinus with the tissues of the patient's own free muscle flap of the thigh.

The most stressful complication was thrombosis of the donor vein that occurred during the first day after the surgery. The possible cause of the thrombosis was damage of the facial vein incurred during its isolation, which resulted in narrowing of the vessel's lumen. Sequential thrombectomies were performed on the first, second, and third day to restore the blood flow. A catheter was introduced to the right external carotid artery for perfusion of the flap with low-molecular weight heparin; however, this did not have the desired effect, and on the fourth day transplantation of a 12-centimeter part of his own vein from the lower leg was performed. The volume of tissue loss due to ischemia was insignificant and localized in the columella.

False aneurysm of the donor artery on the right was diagnosed at 52 days, situated where the artery emerged from the subcutaneous tunnel in the projection of the nasal bone of the allograft. The cause of this complication was associated with 2 factors: the different pressure of the surrounding soft tissues on the artery in the tunnel, and vascular wall deinnervation, which resulted in a decreased tone. Regression of the symptoms was observed on the 74th day after the face allotransplantation.

Rehabilitation

The tracheostoma was removed 12 days after the surgery. By 4 months, complete restoration of nasal breathing was noted, and tactile sensitivity appeared in the allograft; despite the absence of sutures of the sensory nerves, sensation in the skin allograft was slightly different from that in the surrounding tissues of the recipient.

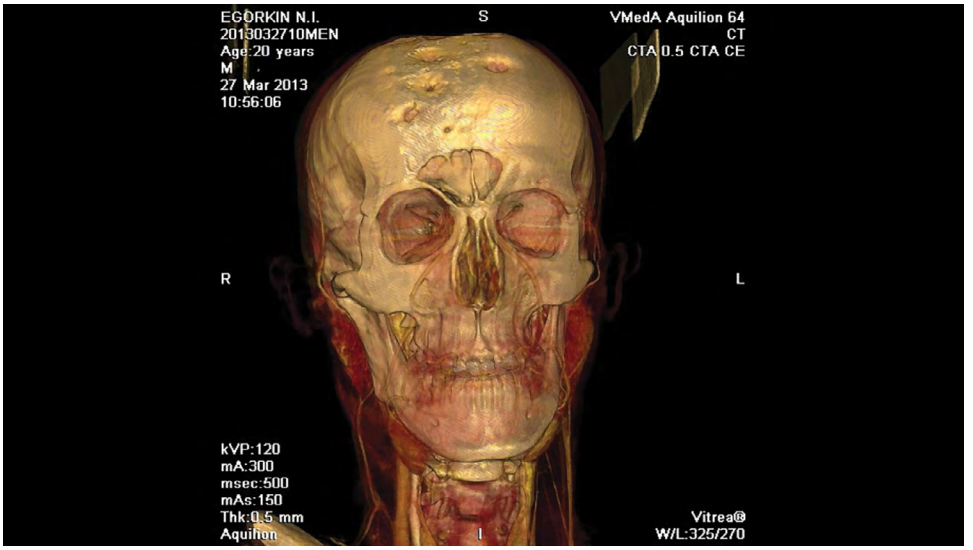

Fig. 9. Computed tomography (CT) of the facial skull bones before the facial allotransplantation surgery.

Psychological Adaptation

Based on information obtained from the study of clinical cases that are similar to this one, experts assume that post-surgical reactions may be due to inconsistencies between the patient's ideas about his new appearance and the real appearance, and include strong emotional reactions to the new face, subsequent negative feelings and depression.[8,9]

In contrast to the predicted emotional manifestations caused by potentially stressful conditions at the moment the patient saw the transplantation results for the first time, our patient showed calmness in relation to the new face. There was also no delayed reaction to the stress. The patient did not show behavioral changes, and his emotional condition did not change.

After the operation psychologists were able to establish contact with the patient, which was greatly facilitated by long-term psychological conversations. The experts were able to assess changes in emotional condition, and the cognitive and behavioral ways of reacting and interacting with the world, as well as the internal picture of the disease. Based on psychodiagnostics, a complex of psychocorrectional measures was developed, and body-oriented psychotherapy, techniques aimed at relaxation, and therapeutic art approaches were applied.

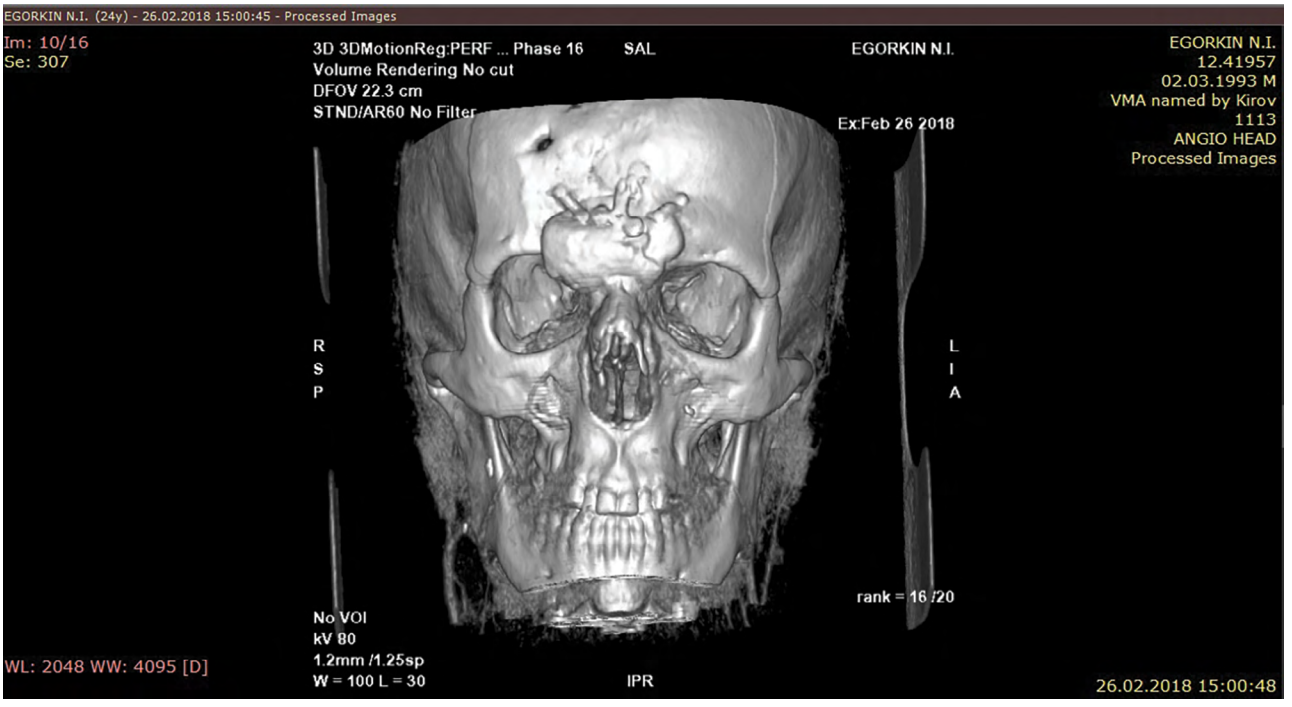

Fig. 10. Computed tomography (CT) of the facial skull bones 33 months after the facial allotransplantation surgery.

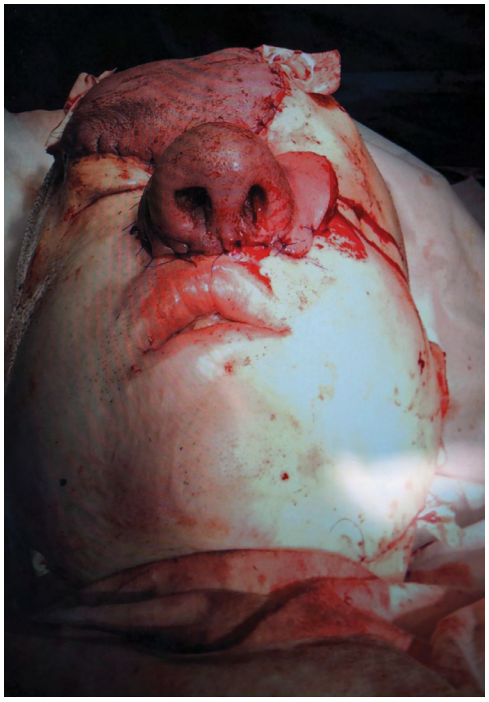

Fig. 11. Appearance of patient E at the final stage of the facial allotransplantation operation.

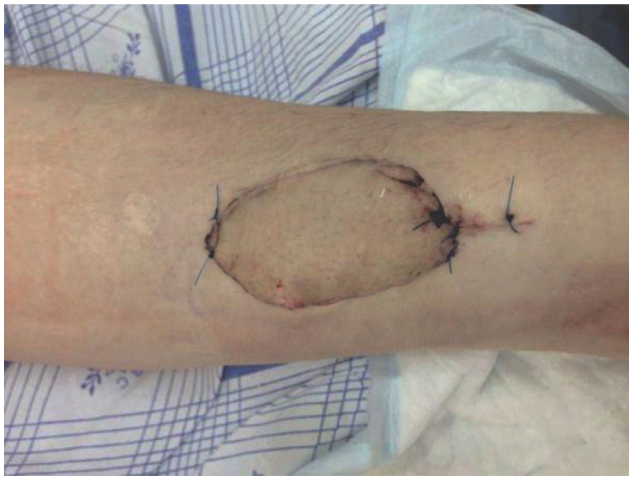

Fig. 12. Appearance of the forearm of patient E after the transplantation of Chinese flap.

Condition of the Patient at the Present Time

One year after the partial face allotrasplantation, the patient underwent rhinoplasty aimed at reduction of the volume of tissues at the end part of the nose and restoration of the columella (Fig. 14).

In June 2017, graft-versus-host disease of mixed humoral-cellular type occurred. In the course of treatment, the immunosuppression regimen was corrected, with a switch to the tacrolimus group medicine Advograf. The current immunosuppression protocol is as follows: Advagraf 8 mg/day, oral Myfortic 720 mg twice a day, and Solu-Medrol 4 mg once a day.

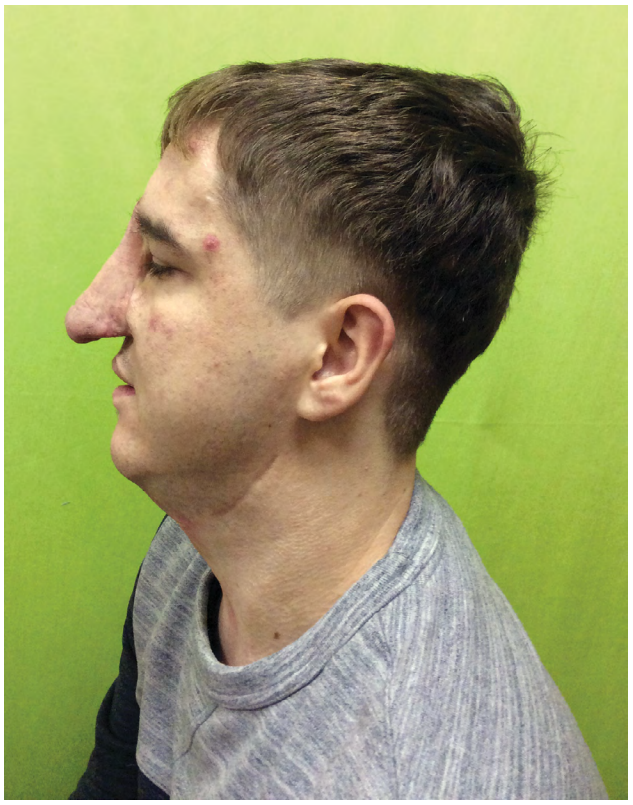

Fig. 13. Appearance of patient E 2 years post partial facial allotransplantation operation.

Fig. 14. Appearance of patient E. 3 years post partial facial allotransplantation operation.

Complete social rehabilitation of our patient has now been achieved. He attends an institution, works, and has a family (Fig. 15).

DISCUSSION

There are defined indications for facial transplantation, the first significant systematization of this knowledge being the monograph by Siemionow.[5]

In our case, general and target indications for the partial facial allotransplantation were: motivation, stabilization of long-term outcome of the injury, complete understanding of the consequences of the injury, stable emotional-volitional and intellectual-mental characteristics of his personality, age, the limitations of autoplasty (posttraumatic changes in the soft tissues of the right hand, forearm, upper arm, scapular areas, right and left thighs, right lower leg, sacrum, and combined deformity of toes I, II, and III on both feet), extensive area of facial defect (about 65%), almost total defect of the nose and external wall of the frontal sinuses, soft-tissue defect of the forehead, cicatricial deformity of the eyelids, the right half of the face and neck.

Our experience of performing stages of the international protocol for preparation for facial allotransplantation, with composite hemifacial transplantations and anatomical studies, will help us to be able to use this knowledge effectively in future clinical practice.

In the course of the clinical implementation in this case, we have found that explantation of the allograft should be performed according to the "full-face" model, regardless of the variant of the transplanted allotissue complex. This approach allowed us to adapt the resulting complex of tissues maximally to the recipient, as well as to save the donor vascular system for carrying out adequate perfusion at the stages of allograft explantation and

IMMUNOSUPPRESSION PROTOCOL	
MMF (Myfortic)	1. 360 mg per os, a single dose before the surgery; 2. 720 mg per os, bid 3. The monitoring of MMF products concentration in the serum was not performed.
Cyclosporine A (Sandimmun Neoral)	1. 6 mg/kg/day, per os, divided into 2 doses. 2. Monitoring of the serum concentration: 2 times a week. 3. The target concentration on Days 1-30 is 200-300 ng/mL. 4. After Day 30: 180-200 ng/mL.
Interleukin-2 receptor antagonist (Simulect (basiliximab))	1. Intraoperatively, 20 mg iv drip for 20 min.; 2. On the 4th day - 20 mg, iv drip.
Methylprednisolone (Solu-Medrol)	1. Intraoperatively (before including the graft into the bloodstream) 500 mg, iv drip. 2. On day 2 - 250 mg, iv drip; 3. On day 3 - 125 mg, iv drip; 4. On day 4 - 125 mg, iv drip;
Methylprednisolone (Metipred)	1. Since Day 5 - 30 mg per os, daily. 2. Day 10-20 - 20 mg per os, daily. 3. Day 20-30 - 16 mg daily.
Antiviral therapy:	1. Valcyte 900 mg/day; 2. Monitoring of the CMV viremia.
Prevention of pneumocystis pneumonia:	1. Biseptol (Co-trimoxazole) 480 mg, bid.

Fig. 15. Schematic of immunosuppressive therapy at different stages of partial face allotransplantation.

subsequent conservation. In addition, it helped us to have a reserve of plastic material.

The "full-face" model is the most favorable from an aesthetic point of view; however, in our case, it had extremely limited indications due to the high risk of an unfavorable functional result and allograft rejection.

In view of the characteristics of the donor-recipient system, the simulated composite alloflap in our case included the external wall of the frontal sinuses, soft tissues of the forehead, and the whole nose with adjacent tissues of the midface. Blood supply to the allograft was ensured by using the right facial artery and left facial vein system. This model was satisfactory for achieving the functional and aesthetic goals of face reconstruction in our patient and allowed us to minimize the immunosuppressive load.

CONCLUSIONS

Consistent compliance, with the international protocol for preparation for facial allotransplantation, including performing of experimental allotransplantation, cadaver studies, and 3D modeling, and improvement of organizational and legal regulations, allowed us to successfully perform the first case in Russia of facial allotransplantation in a patient who had suffered electrical burns, and to achieve restoration of aesthetic and functional parameters of the face and the social rehabilitation of the patient.

Facial allotransplantation is not only a viable alternative to conventional reconstructive techniques—in some clinical situations, it is the only choice.

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ACKNOWLEDGEMENTS

The authors would like to express their sincere condolences to the relatives of the deceased donor and to express gratitude, on behalf of themselves and the recipient. It is thanks to their consent that we were able to save a person's life.

More than 200 medical and biological specialists, and pilots of the Ministry of Defense, all played a part in saving the life of the patient. Without their help, this surgery would not have been possible.

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