

Facial Transplantation: The Next Frontier in Head and Neck Reconstruction

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KEYWORDS

• Reconstruction • Microvascular • Face
• Transplant • Surgery

Facial reconstruction of extensive defects poses a unique surgical challenge that must take into account the skin color, texture, and complex movement associated with facial expression. Failure to account for these considerations can be dehumanizing. More challenging and equally important are the functional aspects of the face that often are compromised after trauma, burn injury, or surgical resection. The functional consequences of incomplete restoration of the eyelids and the lips can lead to blindness and oral incompetence.

Conventional approaches to facial reconstruction are largely dictated by the extent of the defect. Although smaller defects may be amenable to local flaps, more extensive defects often require free tissue transfer or split-thickness skin grafts. These techniques may suffice to provide coverage; however, they fail to provide a color or texture match and, more importantly, are unable to restore function and movement. Microvascular free flap reconstruction has played an important role in providing coverage for extensive defects that otherwise may represent a risk for infection; however, the cosmetic and functional results are suboptimal. More importantly, microvascular free tissue transfer is a technique that has opened the door to considering the role of microvascular

allotransplantation for the management of extensive facial defects.

Composite tissue allotransplantation (CTA) refers to the transplantation of a heterogeneous group of tissues, including skin, muscle, nerve, and, in some cases, bone. Unlike solid organ transplantation, CTA involves the transplantation of a variety of different tissues each with its own unique antigenic profile. As a result, immunosuppression to prevent rejection can be complex and not always achievable for prolonged periods without leading to systemic toxicity. Skin-bearing transplants are particularly unique because of the high level of antigen-presenting cells residing within the dermis. To prevent rejection, high doses of immunosuppression often are required. Such high levels of immunosuppression are associated with acute and chronic toxicities. Earlier experiences and lessons learned from hand transplants performed in France, China, and Louisville, Kentucky, highlight the multifaceted and complex nature of maintaining a successful transplant.¹ Failure to comply with the immunosuppressive regimen, as demonstrated by the hand transplantation experience, inevitably leads to rejection and graft loss.

The issues surrounding the ethics and science of facial transplantation are interesting and

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controversial. As transplant immunology is understood better, the potential applications are limitless. Although the ethics of such programs are actively debated, the role of microsurgery in achieving such transplantations is essential.

HISTORY

Early experiences with CTA involved hand transplants, first performed in Lyon, France, and Louisville, Kentucky, in 1998. The recipient of the first "successful" hand transplant, which recently underwent amputation because of rejection, stated that he experienced pain and burning sensations with no normal sensation in the hand.¹ The patient also became emotionally detached from the allograft and could not incorporate it into his own identity. Further reports from China, in which approximately a dozen unilateral and bilateral hand transplants were performed, revealed that most cases have undergone chronic rejection with progressive loss of function resulting from lack of compliance with immunosuppressive medications and consistent medical follow-up. At least two patients underwent amputation of their transplanted hands.² Despite the challenges faced in the area of hand transplants, interest in facial transplantation continues to grow.

In December 2002, at a meeting of the British Association of Plastic, Reconstructive and Esthetic Surgeons, British surgeon Peter Butler announced his intention to perform facial transplantation. This ignited widespread public interest and debate over the implications of facial transplantation. In November 2003, reports from a working party of the British Royal College of Surgeons and the French National Consultative Ethics Committee for Health and Life Sciences concluded that the risks outweighed any perceived benefits and that performing facial transplantation was considered highly experimental until more research was conducted and the rate of complications improved.^{3,4} In October 2004, Maria Siemionow and colleagues⁴ at the Cleveland Clinic obtained institutional review board approval for facial transplantation in humans.

The first partial face transplant was performed in November 2005. A woman was traumatized by a severe dog bite that resulted in amputation of portions of her middle and lower face (Fig. 1A). A team of surgeons in Lyon, France, led by Jean-Michel Dubernard, transplanted the allograft, which included skin, facial muscles, vessels, and nerves.⁵ The immediate postoperative course was uneventful. During the third week, mild clinical signs of rejection were encountered and controlled

with boluses of steroids. Semmes-Weinstein testing revealed sensory recovery by the 14th postoperative week and at 4 months post surgery the patient had an acceptable aesthetic result (see Fig. 1B). Motor recovery followed with improved facial movement at 18 months. A follow-up report deemed the operation a success with respect to function, aesthetic appearance, and psychologic acceptance by the patient.⁶

To date, three partial face transplantations have been performed worldwide. A second case of partial face transplantation was reported in China of a 30-year old man who had been severely injured in a bear attack (Fig. 2A). After several unsuccessful reconstruction attempts, the patient underwent CTA. In the postoperative period, the patient had three acute rejection episodes and hyperglycemia, which were managed by an adjustment in immunosuppression protocol, pulsed steroid therapy, and insulin therapy. After transplantation, the patient underwent adjunctive reconstructive procedures to improve his appearance (see Fig. 2B). At 2 years post transplantation, the patient had adequate sensory and thermal discrimination but facial nerve function was poor. This was attributed to the severely damaged condition of the recipient's facial nerve despite performing a neural anastomosis.⁷ In February 2007, a team led by Laurent Lantieri performed the third transplantation on a 27-year-old man who suffered from neurofibromatosis type 1 (Fig. 3A). The patient had a massive plexiform neurofibroma that was infiltrating the central and lower portions of his face resulting in bilateral facial paralysis and severe disfigurement. During transplantation, bilateral arterial, venous, and neural anastomoses were performed. The patient experienced two episodes of acute rejection (days 28 and 64) and cytomegalovirus viremia, which were managed by steroid pulse therapy and intravenous foscarnet.⁸ Quantitative sensory testing and electroneuromyographic examination at 12 months showed signs of motor and sensory reinnervation.

Facial transplantation has garnered tremendous interest during recent years, since the first reported case in France in 2005, fueled by reports in the popular media. The controversy over the ethical, immunologic, and psychologic issues, however, remains.

THE ROLE OF MICROSURGERY IN COMPOSITE TISSUE TRANSPLANTATION

Not unlike the sentinel work performed by Taylor demonstrating the vascular territories of candidate donor sites for free tissue transfer to achieve facial transplantation, has it been necessary to



Fig. 1. The first partial face allograft. (A) Preoperative image from June 2005. Patient was traumatized after a severe dog bite with amputation of the middle and lower portions of her face. (B) Postoperative image 4 months after the first partial face allotransplantation. (Reprinted from Devauchelle B, Badet L, Lengelé B, et al. First human face allograft: early report. *Lancet* 2006;368:204. Copyright [2006]; with permission from Elsevier.)

understand the vascular territories of the face.⁹ Early work evaluating the facial vessels demonstrated that although a hemifacial transplant can be performed using the ipsilateral facial artery and vein, a complete facial transplant (**Fig. 4**) requires bilateral facial vessels for revascularization.^{10,11} The microsurgical aspects of allotransplantation essentially are the same as those used in free tissue transfer. The viability of the allograft is dependant on the flow through the facial artery and facial vein.¹² Several techniques have been described using the external carotid artery or the facial artery; however, like free tissue transfer, the more blood flow to the flap, the less likely ischemia ensues.

Unique to facial transplantation are the issues of immune-mediated rejection and motor reinnervation. Acute rejection must be prevented at all costs. An early rejection episode may result in acute vascular thrombosis at the site of the microvascular anastomosis or microthrombosis in the capillary system located in the distal areas of the

flap. As a result, patients are treated with a strict immunosuppressive regimen that must be maintained for the life of the patient if the graft is to be preserved.⁶ Monitoring of the flap perfusion can be accomplished with an external temperature probe, Doppler probe, or skin prick.

Unlike conventional free flap reconstruction, facial transplantation usually requires motor and or sensory reinnervation. Although this is used occasionally for free flap reconstruction of the head and neck, it is commonly used for facial transplantation to provide facial sensation, tone, volitional movement, and oral competence. This requires that a surgeon is comfortable with micro-neural surgery. An 18-month follow-up after facial transplantation performed by Dubernard and colleagues⁶ demonstrated that the patient was able to eat and drink almost normally by the end of the first postoperative week with mild leakage during drinking from her mouth. The oral incompetence had resolved by 12 months. Sensory recovery as assessed by Semmes-Weinstein tests



Fig. 2. A partial facial allotransplantation performed in China in 2006. (A) A man severely injured in a 2004 bear attack. (B) Twenty months post transplantation. (Reprinted from Guo S, Han Y, Zhang X, et al. Human facial allotransplantation: a 2-year follow-up study. *Lancet* 2008;372:632. Copyright [2008]; with permission from Elsevier.)

(light touch sensation studied using static monofilaments) demonstrated that sensory discrimination was recovered and hot and cold sensation nearly normal at 4 months and normal at 6 months over the entire graft.

IMMUNOSUPPRESSION

Unlike other common solid tissue transplants, such as kidney and liver, CTA, like facial transplants, is histologically heterogeneous and contains tissue components that express different antigenic forms. Therefore, allotransplantation mandates substantial lifelong immunosuppression to prevent rejection. Failure of or noncompliance with the regimen could lead to devastating results with the loss of the transplanted face.¹³ Unlike most solid organs transplants, which usually are more tolerant of acute rejection, facial CTA is less able to tolerate rejection, and acute rejection may lead to scarring and dysfunction of the graft or fulminate rejection and graft necrosis.¹ Over the past 4 decades, several significant developments in immunosuppression protocol have allowed for long-term survival of partial and complete allotransplanted organs, ranging from 60% to 90% at 5 years depending on the transplanted organ.¹⁴ Achieving

a balance between overimmunosuppression and underimmunosuppression requires an appreciation of other factors, including pretransplant morbidity, pre-existing disease status, nutritional status and post-transplant immunomodulating viral infections.

CTA immunosuppression protocols have been less developed until recently because of the notion that these types of tissue transplants are not essential for survival. Currently, the most commonly used maintenance immunosuppression in kidney transplant recipients in the United States is a tacrolimus, mycophenolate acid, and corticosteroids combination, which also has been successfully used in recent experimental hand and face transplantations.¹⁵ Immunologic risk data, published in 2004 in "Facial Transplantation: A Working Party Report from the Royal College of Surgeons of England,"¹⁶ estimate the likelihood of graft loss at approximately 10% from acute rejection within the first year and of significant loss of graft function from chronic rejection at approximately 30% to 50% of patients over the first 2 to 5 years.¹⁷ To monitor for rejection, Duberand and colleagues⁶ used a concomitant radial forearm free flap allograft placed into the submammary fold. This was used as a sentinel



Fig. 3. CTA performed on a patient who had neurofibromatosis type 1. (A) A man who had a massive plexiform neurofibroma infiltrating the central and lower portions of his face. (B) One year post transplantation. (Reprinted from Lantieri L, Meningaud JP, Grimbert P, et al. Repair of the lower and middle parts of the face by composite tissue allotransplantation in a patient with massive plexiform neurofibroma: a 1-year follow-up study. *Lancet* 2008;372:640. Copyright (2008); with permission from Elsevier.)

graft for skin biopsies to limit damage to the grafted face.

ETHICAL CONCERNS

At the center of the ethical debate in facial transplantation is the question, Does potentially improving a patient's quality of life justify the potential long-term risks involved with immunosuppression?¹⁵ The complications of lifelong immunosuppression are well defined and significant side effects, such as increased rates of cancer, infections, and nephrotoxicity, are potentially life-threatening. The etiology of post-transplant malignancy is believed multifactorial in nature and presumably the result of impaired immunosurveillance of neoplastic cells and depressed antiviral immune activity.¹⁸ Recent renal transplant experiences with tacrolimus, mycophenolate mofetil, and steroids combination, which is the current immunosuppressive regimen in CTA, revealed that the cumulative incidence of cancer is lower at the early time point of 3-year follow-up. To date, none of the hand transplant recipients has developed cancer.¹⁵

The majority of patients who have had a transplant have an infection as a result of immunosuppression. Opportunistic infections include viral infections, fungal infections, and *Pneumocystis carinii* pneumonia. Over the past decade, improved selectivity of immunosuppressive regimens, the availability of new antiviral and antifungal agents, and improved diagnostic accuracy have played a role in decreasing the incidence and severity of post-transplant infections.¹⁷

As the concept of quality of life for patients has become more important, acceptance of allotransplantation for these less critical transplants has grown significantly. This acceptance has increased as techniques for immunosuppression have become more specific and targeted and have fewer side effects. The ideal immunosuppressive agents target tissue and organ that are transplanted and allow acceptance of the transplanted part without having any other effects on the recipient's tissue. Thus, the ability of a recipient to combat residual cancer or any potential metastatic sites remains intact and this form of targeted immunosuppressant would have no negative effects on the outcomes of the cancer.¹⁴



Fig. 4. A complete facial allotransplantation would require bilateral facial vessel and neural anastomoses for revascularization and successful transplantation. (Courtesy of Christine C. Kim, Chicago, IL.)

The development of these types of agents will revolutionize microsurgical reconstruction because they would allow transfer of previously unreconstructable, specialized tissues using well-described microsurgical techniques and would maximize the aesthetic and functional results of head and neck reconstruction. The development of highly immunosuppressive agents remains the principal obstacle to taking microsurgical reconstruction to the next level in CTA.¹⁴

Careful patient selection is critical to the final success of facial transplantation. Failure to comply with the immunosuppressive regimen of medications can have catastrophic results leading to rejection of the facial part. Poor selection of patients could have a negative effect on the future of this reconstructive procedure and fuel ethical and legal disputes. Guiding principles, published by the American Society of Plastic Surgeons and the American Society for Reconstructive Microsurgery, consider facial transplantation an experimental procedure, urging that facial transplantation be attempted only by multidisciplinary teams under institutional review board-approved research protocols.¹⁶ Steps are needed

to balance the risks and benefits of this highly controversial procedure.

FUTURE DIRECTIONS AND CONCLUSION

Although the technical aspects related to microvascular and microneural surgery required to initiate a transplant are well worked out, donor-specific immunotolerance regimens need to be explored further before facial transplantation can be offered to patients routinely. Current immune strategies to achieve tolerance induction include irradiation, donor bone marrow transfusion, intrathymic injection of donor cells, and antibody-based therapies.¹ Future research will be directed in these areas and with progress in nontoxic regimens, there is little question that facial transplantation will play a role in the future of facial reconstruction.

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