

REVIEWS

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Face Transplantation – New Possibilities and Risks

Przeszczep twarzy – nowe zagrożenia i korzyści

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Abstract

As a new achievement in composite tissue grafting, partial face transplantation needs to be reconsidered from a medical and ethical point of view. The aim of this paper is to present the benefits and risks involved in face transplantation. The crucial facet is the attitude of physicians with regard to augmenting the quality of life at the expense of life-span. The technical aspects include selection of the recipients, the operational approach, immunosuppressive therapy, and the feasibility of alternative reconstructive methods (*Adv Clin Exp Med* 2007, 16, 2, 323–328).

Key words: face, transplantation, immunosuppression, reconstructive surgery, quality of life.

Streszczenie

Częściowy przeszczep twarzy, nowe osiągnięcie transplantologii, wymaga rozważenia wielu kwestii zarówno medycznych, jak i etycznych. Celem pracy jest przedstawienie korzyści oraz zagrożeń, na jakie są narażeni biorcy. Podstawowym problemem etycznym jest stanowisko lekarzy wobec polepszenia osobom oszpeconym jakości życia kosztem jego długości. Do technicznych zagadnień związanych z przeszczepem twarzy należą: wybór biorców, sposób operowania, leczenie immunosupresyjne oraz dostępność alternatywnych metod rekonstrukcyjnych (*Adv Clin Exp Med* 2007, 16, 2, 323–328).

Słowa kluczowe: twarz, przeszczep, immunosupresja, chirurgia rekonstrukcyjna, jakość życia.

Of all physical handicaps, facial disfigurement causes the gravest social consequences. Face injuries may result in depression, social isolation, and increased risk of suicide [1]. While a limb deformity or its lack elicits pity or sympathy, face disfigurement arouses uneasiness, fear, and the wish to remove it from one's sight [2, 3]. Until November 2005, the only possible way of managing this deformity was conventional or microsurgical reconstruction using skin and bones from other parts of the body, usually the arm. However, for many reasons the results of this technique are far from satisfactory. The first documented face transplant, performed in Amiens, France, created new perspectives for this numerous group of patients. The operation was performed on a 38-year-old woman who had lost the nose, the upper and lower lip with adjacent parts of the cheeks, and the chin due to a dog attack [4]. The transplant

was carried out by Professor Bernard Devauchelle in spite of an earlier report of the Royal College of Surgeons of England (issued in November 2003) [5] and a report of the Comité Consultatif National d'Ethique (issued in February 2004) [6]. According to these reports, face transplant at present is associated with too significant a risk, outweighing possible benefits.

Thanks to the large number of transplants performed since 1954 (the first renal transplant), incredible progress has been made in the field of transplant medicine [7]. Nevertheless, the risk of rejection due to the operational technique continues to be about 5% [5], and immunosuppressant therapy has serious side effects. In particular, there are many unknowns concerning composite tissue allografts, in instance of the upper limb or the face. The first forearm transplant was carried out in 1998 in Lyon, France, on an ex-convict by

Professor Dubernard (who seven years later supervised the first face transplant and was responsible for the postoperative treatment) [8, 9]. In the following eight years, 33 such operations were performed in hospitals all over the world. In this way, great experience has been gathered in grafting skin, muscles, and their vasculature and knowledge about immunosuppressive therapy has been deepened, which allowed the face transplant to be carried out [10]. Nevertheless, not only have the controversies continued, but they have intensified due to the unclear circumstances of the French procedure. Also, many questions concerning medical, ethical, psychological, and socio-economic facets have not been answered.

Recipients and Donors

All over the world, thousands of people suffer face injuries [11]. The most common causes include burns, craniofacial tumor excisions, animal attacks, and gun-shot wounds (among which the most devastating are shotgun wounds). It is commonly admitted that the recipients should be only those severely disfigured, who have lost most of their faces [12]. Moreover, according to Butler, the right patient should be somebody who has not only lost his appearance, but also the normal functions of the face, i.e. has no ears and nose, cannot open his mouth, and the eyelids do not close properly, leading to eye infections and drying of the cornea. In such a case, a face transplant would not only improve appearance, but above all it would restore quality of life. Butler states that “the first recipient should be an adult who had already become accustomed to his disfigurement because he would likely accept his new face as well as returning to the previous state in case of operational failure” [13]. Also, it seems that the recipient should have enough healthy skin for reconstruction procedures if the transplant fails. This may exclude those patients who have already undergone many reconstructive operations.

This belief differs significantly from the original notion that the perfect recipient would be a child aged from 1.5 to 5 years old because in this age range, face recognition does not play a major role. This idea, however, was abandoned after considering the consequences of asking parents of a brain-dead child for his face [13]. Another important reason why a child does not seem a proper recipient is the unpredictable behavior of a graft during the growth of a young organism, difficulties in therapy compliance, and the presence of feasible standard reconstructive techniques for this age range [14].

The problem of finding a donor is not limited to the youngest patients, as a survey conducted by Butler at his hospital in the United Kingdom indicates. He chose 120 persons – 40 doctors, 40 nurses, and 40 laypersons – and the majority of them admitted they would accept somebody’s face, but *not a single person* would agree to giving away their own face [13]. Harvesting the face makes the grieving ritual of an open casket and public viewing of the body virtually impossible, which would probably discourage the family from consenting to giving away the face of the deceased [15]. In such circumstances, the status of the face as an allograft is still unregulated in transplantation law.

The great problem of immunosuppressive treatment should be taken into consideration when selecting the recipient. Besides having facial disfigurement, the recipient should be healthy enough to tolerate the side effects of immunosuppressive drugs. Another important matter is the material status of the recipient. The first two face graft recipients, a divorced single mother of two and a Chinese peasant, did not cover the expenses of the operations themselves (the operation of Li Guoxing was funded by the military Xijing Hospital and the Natural Conservancy Foundation [16]). It should be assumed, however, that as soon as face transplants stop being a mass media sensation, the recipients will have to pay for the procedures and the subsequent immunosuppressive therapy themselves. At present, a year of such therapy costs tens of thousands of American dollars. If the national health insurance systems do not include face transplant, only members of the upper socioeconomic class will be able to afford these procedures.

Patient compliance, expressed in the change in life style and taking prescribed drugs, is extremely vital for the success of a transplant. The importance of this fact is exemplified by the first recipient of a partial face transplant: against Professor Dubernard’s advice, the patient started to smoke again, obviously increasing the risk of rejection [17]. It is estimated that 15–18% of recipients are in compliant, most often the young and those from the lower socioeconomic classes. This fact is explained by inaccurate, exaggerated expectations of the results [5]. This was probably the case of the first forearm recipient, who was disappointed with the low grade of the graft’s functionality and thus discontinued the immunosuppressive therapy and rehabilitation [18]. The scale of this phenomenon suggests the necessity of introducing psychological assessment in recipient selection that would predict the chances of therapy compliance.

Alternative Treatment

Until recently, patients with face injuries could be treated by replanting the avulsed part [19] using tissues from other parts of the body [20] or using prosthetics [21]. The first patient to undergo a face replant was a nine-year-old Indian girl whose face and scalp was avulsed in 1994 by a threshing machine. The next two cases were described in the USA and Australia [22]. Nevertheless, a replant as a best option for the patient with face injury is very often impossible. Thus, in order to fill tissue losses, surgeons move skin and muscles from other parts of the body and shape them into the lacking parts of the face. However, the skin of the face has a unique texture, color, and underlying muscle layer thanks to which it is not a mere mask, but a functioning organ. Normal eating, talking, and closing the eyes is impossible without facial movement. Reconstructing a deformed face, usually using the lateral arm flap, is so difficult that burn victims may undergo as many as 50 operations, with only a poor result [22]. The greatest disadvantages of reconstruction concern its main goals: the esthetic effect is not acceptable, the lost functions are not recuperated, and the face has no expression [5]. All this results in a mask-like effect. Transplant, on the other hand, would be a single operation, and thanks to the nerve and muscle grafts it would allow recovering a normal appearance. The recovery of expression and sensitivity would be partial because the capacity of neuronal regeneration is estimated to be about 50% [22].

The future treatment of third-degree burns, congenital skin diseases (for instance epidermolysis bullosa), and skin loss after tumor resection will be probably based on skin engineering. Material obtained by this technique should have a few special features because it will be autologous (which would allow abstaining from immunosuppressive therapy), porous (permitting cell migration), and bioinductive (assuring correct angiogenesis). Skin implants obtained by means of skin engineering may be genetically enriched with genes coding for protease inhibitors or for proteins responsible for the regeneration of the body integument. These genetic modifications would allow accelerating the healing process in such adverse conditions as diabetes, corticosteroid treatment, or chronic inflammations. Similar genetic manipulation may be used to minimize the risk of neoplasm development [23].

Technique

A total facial transplant requires a complete harvesting of the face. The margins of such a flap would follow the hair line in front of the ears down

to the mandibular border. This flap might include the eyebrows, eyelids, nose, and mouth. Besides the skin and its thin adipose layer, the surgeon will also harvest the vessels, nerves, mimic muscles, and nasal cartilage [17, 22, 24]. As Butler states, the point is that "Once into the sublayers of musculature and bone, there is an increased risk of both rejection and infection, and the problem of having to fuse the donor's facial nerves with those of the recipient, whose face would have already been removed. That, however, does not guarantee the proper synaptic relays between the nerves and could result in what is known as dyskinesia, an internal misfiring of nerve signals that could leave patients twitching uncontrollably or smiling when they mean to frown." [13]. The vessels should be reattached as proximally as possible. This is why anastomoses will be made at the levels of terminal branches of external carotid artery, superficial temporal artery, internal maxillary artery (these vessels provide blood supply for the upper third of the face and its deeper structures), facial artery (which supplies blood for the rest of the face), and ophthalmic artery (blood supply for the orbicular region). Venous drainage will be assured by anastomosing the external, internal, and anterior jugular veins into which drain the superficial temporary, facial, inferior labial and mental veins, respectively [25].

The microsurgical skills necessary for fast and efficient facial allografting were obtained during mock transplants on cadavers. The surgical team of Cleveland Clinic, USA, performed 10 dissections of human cadavers (eight of which were used as donors, two as recipients). The time needed to harvest a facial flap was 4 h. The mean length of the donors' external carotid artery was ca. 5 cm, the facial and external jugular veins 3 and 6 cm, respectively, and the prepared supraorbital, infraorbital, mental and great auricular nerves 1.5, 2.5, 3, and 6 cm respectively. Time of harvesting a monoblock, full-thickness skin graft from the recipients' faces was ca. 45 min. Anchoring a face graft on the recipients' skulls took 20 min. Total transplant time without forming vascular and nerve anastomoses was 5 h 20 min [26]. Based on these results, some researchers suggested that there should be two teams of surgeons, one preparing the donor, the other the recipient, in order to minimize ischemia time. Using hemostatic agents was also suggested since bleeding significantly increases operation time. Finally, it was advised that anastomosing the veins should precede that of the arteries in order to avoid flap congestion and subsequent bleeding [27].

Like other transplants, the first human facial allograft was preceded by thorough experiments on animals. The first such trials on pigs took place

in the mid 1990s [28]. In 2002 a Columbian team transplanted a snout onto a dog, but the animal had to be destroyed due to rejection [29]. The next step consisted of a successful face transplant in a rat model performed by the above-mentioned surgeons from Louisville, who succeeded in inducing effective immunosuppression with cyclosporine A [30]. The number of experiments on animal models, however, seems to be insufficient for assuring the safety of the facial transplant procedure.

The French team who performed the first partial face allograft anastomosed both the left and right facial arteries and veins, repaired the mucosa of the oral and nasal vestibules, bilaterally joined the sensitive nerves (the infraorbital and mental nerves), and performed a joining of the mimic muscles with the motor mandibular branch of the left facial nerve. Ischemia of the flap lasted 4 h [4].

The next step in a transplant is inducing efficient immunosuppression that prevents rejection and at the same time is not too toxic for the recipient. The experience gained in the field of hand transplant helps in inducing such an immunosuppression [7, 8]. The pharmacotherapy administered to the partial face transplant patient in Lyon in the first stage of the treatment did not differ in the drugs or their doses from the standards used in limb transplants. The immunosuppressive protocol was based on thymoglobulin, tacrolimus (Prograf), mycophenolate mofetil (MMF), and prednisone [31, 32]. Apart from this, the recipient underwent a transfusion of the donor's bone marrow cells twice. The postoperative period was not uneventful; the patient started to eat one week after the transplant, but on day 20 a mild rejection occurred, suppressed with three boluses of prednisone. The physiotherapy was to restore mobility of the mouth, although a passive transmission of muscle contractions was observed soon after the operation [4]. A check-up in the 14th week of rehabilitation confirmed a complete restoration of sensibility in the grafted part of the face [33]. The literature on the Chinese recipient is extremely scarce, but it is known that he underwent the initial postoperative period successfully. Quite promising seems that after six months of observation, no signs of chronic rejection have appeared in any of the recipients [33]. This may be due to the fact that skin has turned out to be no more antigenic than other organs [34].

Ethical and Psychological Aspects

Ethical problems related to face allograft are far more numerous than the mere technical ones. The most important question is whether a compar-

ison between quality and quantity can actually be made. Due to the inevitably toxic immunotherapy, patients with transplanted hands have 80% risk of infection, 20% risk of developing diabetes mellitus type 2, and 4% to 18% risk of neoplasia [35], in addition to the unknown danger associated with chronic rejection. Immunosuppressive therapy's side effects decrease the recipients' life expectancy. In the case of face transplant, the only benefit is improving quality of life at the cost of shortening it. Nevertheless, potential recipients are ready to take the described risks [36]. Another vague point is the patients' informed consent to this experimental procedure. From an ethical point of view it is essential for a patient to know not only the benefits of the therapy, but also all the risks associated with it. Yet transplant medicine is a relatively young branch of science that has had only seven years of experience in composite tissue allografting. This is why one cannot foresee the time of face graft survival. However, it can be predicted that acute rejection will occur in 10% of recipients, while 30–50% of recipients will lose the graft functions within the second and fifth year after the operation due to chronic rejection [5]. In this case a patient with a stable status of mental and physical disability would be converted into one with an unstable, life-threatening condition with extensive wounds and serious psychological consequences [24]. Little if anything is known about the long-term effects of graft-host interactions; therefore a patient cannot be informed in detail about the transplant.

The influence of unscrupulous surgeons may also be a potential threat to the patients. Disfigured persons live in social isolation, are desperate to change their lives, and may fall victim to the overgrown professional ambitions of some doctors. The case of the first face transplant recipient arouses similar doubts. Isabelle D. was mauled by her dog in May 2005 after she had taken a large amount of sleeping pills and had passed out. Her surgeon denied that she had tried to commit suicide [17], although the patient herself had confirmed the information [37]. The disfigured woman had not undergone any reconstructive surgery at all, and in June 2005 she was entered into the transplant waiting list [38]. According to Lantieri, the greatest violation of the rules of clinical research was undoubtedly transplanting the donor's bone marrow to Ms. Isabelle D., i.e. performing a second experiment on her. The basic rule of a clinical trial is to carry out on one patient only one experiment at a time [38].

Similarly to the situation before the first hand transplants, psychologists expressed concerns regarding accepting the donor's identity along with the graft [7]. Nevertheless, computer simulations made in cooperation with journalists from *New*

Scientist and face recognition experiments on cadavers performed in Louisville have dispelled these doubts [39]. After a face transplant, the skin and muscles adjust to the bone structure of the recipient, so a new, hybrid face emerges [13]. Thus any fears about seeing the face of a loved one on a stranger are unfounded. More probable are psychological problems due to the loss of one's own disfigured face. However, surgeons and psychiatrists agree that an appropriate preparation of patients will allow anticipation of the mentioned disorders [40].

Discussion

Due to the associated concerns, the following points should be considered: issues regarding the

legal status of face transplant and including it in the national health services should be addressed; when deciding whether to perform a face transplant, it should be considered whether this procedure is worth such great effort and costs; more meticulous psychological selection is needed because of the high prevalence of patient non-compliance; in order to decrease the psychological pressure of the recipients and their families, they should be assured anonymity; more experiments on animals are indispensable for developing less toxic immunosuppressive protocols; the use of only brain-dead donors significantly decreases the number of faces available for grafting and slows down the progress of transplant medicine; therefore, taking faces from cadavers should be reconsidered.

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