BURNS 36 (2010) 951–958

available at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/burns

Review

Clinical considerations in face transplantation

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ARTICLE INFO

Article history:
Accepted 14 January 2010

Keywords:
Face transplantation
Composite tissue allotransplantation
Facial disfigurement
Facial burn injuries
Reconstruction and immunosuppression

ABSTRACT

Severe facial burns cause significant deformities that are technically challenging to treat. Conventional treatments almost always result in poor aesthetic and functional outcomes. This is due to the fact that current treatments cover or replace the delicate anatomical facial tissues with autologus grafts and flaps from remote sites. The recent introduction of clinical composite tissue allotransplantation (CTA) that uses healthy facial tissue transplanted from donors to reconstruct the damaged or non-existing facial tissues with original tissues makes it possible to achieve the best possible functional and aesthetic outcomes in these challenging injuries. The techniques required to perform this procedure, while technically challenging, have been developed over many years and are used routinely in reconstructive surgery. The immunosuppressive regimens necessary to prevent transplanted facial tissue from rejecting (tacrolimus/mycophenolate mofetil/steroid) were developed for and have been used successfully in solid organ transplants for many years. The psychosocial and ethical issues associated with this new treatment have some nuances but generally have many similarities with solid organ and more recently hand transplantation, both of which have been performed clinically for 40 and 10+ years respectively. Herein, we will discuss the technical and immunological aspects of facial tissue transplantation. The psychosocial and ethical issues will be discussed separately in another article in this issue.

Contents

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0305-4179/$36.00
doi:10.1016/j.burns.2010.01.011

1. Introduction

Advances in aggressive and early treatment of major burns has resulted in increased survival rates but survivors of these injuries are often left with significant residual deformities [1,2]. When the resulting deformities affect the face conventional reconstructive treatments are woefully unsatisfactory. The greatest challenge to reconstructing these deformities is the destruction and loss of the fine anatomically complex facial tissues. The resulting scar formation leads to hypertrophy and contractures that impair facial function and appearance [3]. Functional impairment is particularly debilitating when contractures develop around the mouth and eyes causing oral incontinence, difficulty eating, drinking and speaking in the former and ectropion, corneal ulceration and even blindness in the latter [4–6]. Contractures of the neck can limit range of motion, alter posture and even restrict the airway. Aesthetic impairment involves loss of "normal" facial form and expression which is substituted by deformed eyelids, nose, and mouth causing asymmetry and a typical mask-like appearance. Combined, these functional and aesthetic deformities often cause severe psychological distress and poor quality of life in these patients.

The ultimate goal when reconstructing facial deformities is to achieve normal function and appearance without asymmetry or mismatch of facial tissues. To achieve this, it is important to consider skin quality which differs in texture and thickness in each area of the face for example, forehead skin is different from cheek or nose skin. Split thickness skin grafts are notorious for contractures and color mismatch. While full thickness grafts do not contract significantly, mismatched coloration can still occur, resulting in a patchwork appearance when used for partial reconstruction of the face. When flaps are utilized they may appear bulky, necessitating de-bulking at later stages to achieve symmetry. Added to this, timing of the different interventions is critical to avoid complications. Irrespective of the treatment method employed, in most cases, even the best of conventional techniques and timing often leave the patients with poor functional and aesthetic outcomes.

The recent introduction of composite tissue allotransplantation (CTA) in the form of facial tissue transplantation could potentially solve many of the problems associated with conventional treatments. The possibility of replacing damaged and/or non-existing facial tissue with healthy, well vascularized facial tissue from a donor is unique and holds great promise. To date seven clinical face transplants have been performed by teams in France, China, and the US [7–10]. Two of these have been to treat severe facial burns [11,12]. Early outcomes have been promising suggesting that this new reconstructive treatment could eliminate many of the drawbacks associated with conventional treatments and provide far superior functional and aesthetic outcomes.

In this review we touch on some of the most commonly used conventional treatments for severe facial burns and mention their main shortcomings. We briefly summarize the history of CTA (in a table) highlighting some of the key research and events that in the past 10 years have led to the first clinical face transplants, we discuss some of the key surgical (patient selection, tissue procurement and implantation, functional and aesthetic outcomes) and immunological considerations (acute and chronic rejection, systemic complications) upon which the success of this new treatment depends. Finally, we discuss some of the key issues that must be addressed to move facial transplantation into mainstream medicine and conclude with our views on how this new treatment could impact the way we care for patients with severe facial burns.

2. Conventional treatments and their shortcomings

Current methods to treat severe facial burns aim to replace and restore the disrupted relationship between aesthetic and functional facial units. Restoration of aesthetic units requires matching skin quality (color, texture and thickness) and when possible, planning so that the resulting scars are in areas of shadows thus ensuring a smooth and uniform appearance. For this, suitable skin graft donor sites – that match skin quality – are regions of the neck above the clavicles, shoulders and upper chest areas. In addition to skin grafts from these areas, locally pre-fabricated flaps using tissue expanders can also be used. Subsequent deformities resulting from contractures are generally treated by contracture release, with or without skin grafts, depending on the requirements. Occasionally, deformities involve loss of one or more original facial tissues. For example, when traumatic injuries result in partial or complete loss of the nose, free composite tissue transfers can be used to fill defects. While grafts and flaps do a good job of covering wounds they cannot restore the delicate complex facial anatomy; therefore, the results are a mismatch between the transferred and adjacent original tissues giving a patchwork appearance. Restoration of the functional areas of the face

requires consideration of the surgical anatomy and should include soft tissues and the underlying muscles which together form a functional unit. This is particularly important when reconstruction involves areas of the mouth, nose and the eyes for its optimal function.

Patients who sustain severe facial burns may also have extensive involvement of other areas of their anatomy causing a paucity of graft donor areas. In such circumstances and in cases when satisfactory reconstruction cannot be achieved with grafts and flaps, prosthetics are used as a last resort to cover and disguise the defect.

All of the above mentioned treatments require multiple staged surgeries and protracted rehabilitation over many years and even then in the best of cases only achieve poor facial appearance and function. In summary, conventional reconstructive treatments for severe facial burns are woefully unsatisfactory and leave affected patients with a poor quality of life.

3. Recent research and events that have led to clinical face transplantation

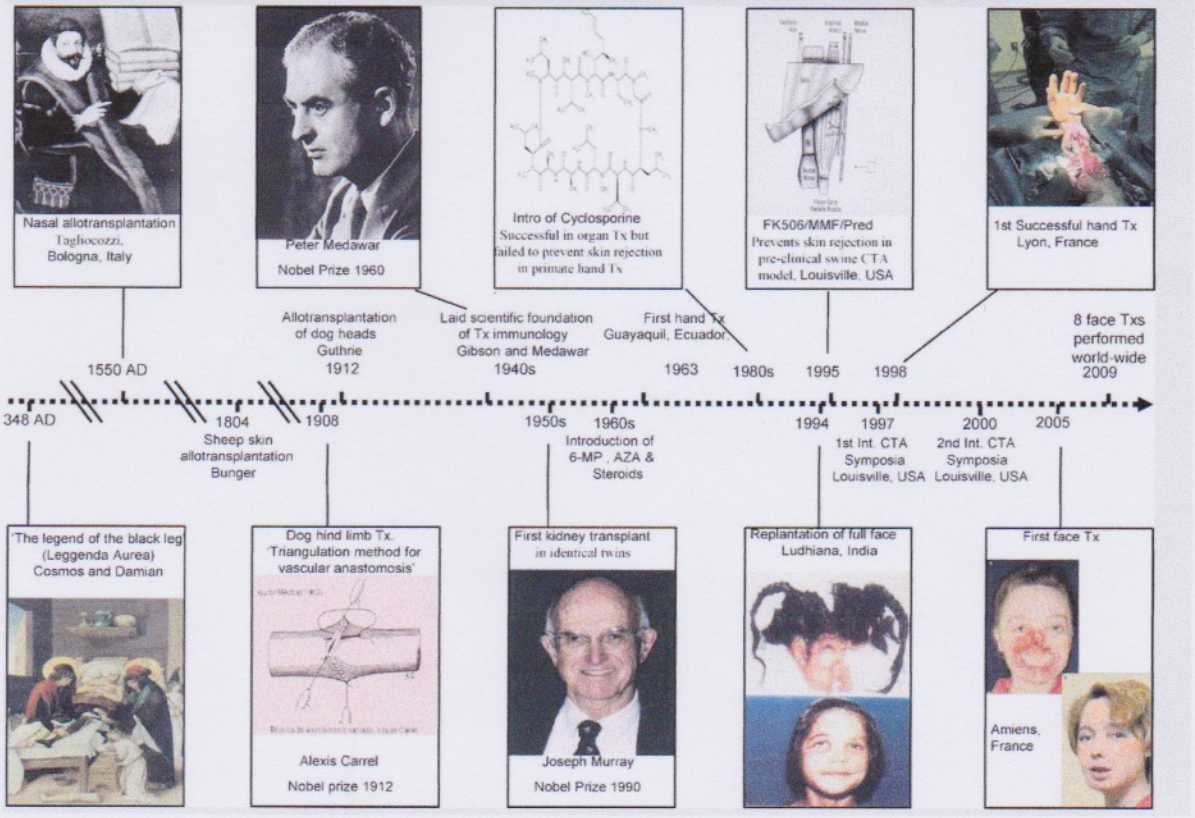
Table 1 provides a historical timeline of key surgical and immunological advances in composite tissue allotransplantation that have led to clinical face transplantation. In the last 10 years, perhaps the most important contribution to the introduction of clinical face transplantation was the success experienced in human hand transplantation. Prior to this, it was thought that the high immunogenicity of skin tissue would not permit this type of transplant.

In 1997 in a series of animal experiments, our team demonstrated that the combination of tacrolimus/mycophenolate mofetil/corticosteroid, then the standard immunosuppression cocktail used in kidney transplantation, effectively suppressed limb rejection in a preclinical CTA swine model [13]. The following year these results led to the use of the same immunosuppression regimen in the first human hand transplants performed in France, the USA and China [14]. Since then, more than 40 clinical hand transplants have been performed by teams worldwide, all using the same drug regimen [15]. In addition to lowering this immunological hurdle, the success of hand transplants also laid the surgical, psychosocial and ethical groundwork for performing human face transplants. In 2005, the first human face transplant [8] was performed in France and today six additional cases have been successfully performed in France, China and the USA [10].

4. Surgical considerations in facial tissue transplantation

In this section we discuss some of the key surgical/technical considerations and touch on functional outcomes in facial

Table 1 – Composite tissue allotransplantation history timeline.



tissue transplantation, beginning with a brief history. In 1902, Alexis Carrel described the successful repair of blood vessels using end-to-end anastomosis technique and in doing so laid the "surgical/technical" foundation for tissue transplantation. In 1912, Carrel was awarded the Nobel Prize in Medicine and Physiology for this pioneering work. Further developments in microsurgical technique and instrumentation made it possible to reattach amputated digits, limbs and tissues and even transplant solid organs between donors and recipients. In 1963, a team of surgeons in Ecuador performed the first human hand transplant (Table 1). In 1994, Thomas et al. reported reattachment of large sections of amputated facial and scalp tissue using microsurgical techniques resulting in 100% tissue survival and good functional and aesthetic outcomes [36]. This and other similar successful attempts to reattach large sections of amputated facial tissue demonstrated the surgical feasibility of face transplantation.

4.1. *Patient selection*

In facial tissue transplantation patient selection is perhaps the most important element upon which success depends and involves a thorough assessment by a multidisciplinary team consisting of reconstructive surgeons, transplant physicians, psychologists and social workers. The most important criteria when selecting potential face transplant candidates is that their facial defect is such that it cannot be adequately reconstructed using conventional methods. Beyond this, the selection criteria for both recipient and donor must include surgical/technical characteristics (skin color, gender), immunological characteristics (blood type, HLA, previous sensitization), psychological characteristics (willingness to undergo the procedure, compliance for life-long immunosuppression), and social characteristics (family support, religious beliefs, etc.).

4.2. *Donor facial tissue procurement*

When a donor is identified and confirmed to meet the pre-established inclusion criteria the recipient is notified, brought to the hospital and prepared for surgery. At the same time, members of the surgical team accompany the solid organ procurement team to retrieve the donor facial tissue. The procurement team must have a thorough knowledge of the recipient's facial tissue needs so that the donor tissues they harvest fulfills, and indeed if possible, exceeds the tissue requirements. The extent of the donor tissue retrieval is based on the facial subunits; in most cases it involves harvesting each subunit with its entire thickness including the mucosa. The facial nerves are dissected, marked and preserved from their exit at the stylomastoid foramen and the facial vessels from their origin including a part of the external carotid artery and jugular vein [16]. Harvesting the facial tissue can require several hours.

4.3. *Facial tissue implantation*

Pre-operative preparation of the recipient is commenced as soon as a donor has been identified and involves excision of scar tissue while carefully identifying and marking all the recipient structures to which the donor tissue will be fitted and attached. This dissection can be difficult because the tissue underlying the scar is well vascularized and oozes copiously during scar excision. In addition, the disrupted anatomy makes it difficult to identify vital structures such as nerves, vessels and muscles. Often the nerves and muscles are severely damaged, atrophic or hypertrophic, either from the original burns or secondary to the scarring from numerous reconstructive procedures performed over the years.

The first priority when implanting facial tissue is to minimize ischemia time by reattaching the donor and recipient vessels. Facial tissue has a rich interconnected vascular network. This has been demonstrated in emergency cases where large sections of amputated facial tissue have been successfully reattached and reperfused using only a single facial vascular pedicle [17]. In the case of facial tissue transplantation, where the conditions of implantation are planned and performed under optimal conditions multiple vessels will be anastomosed assuring good perfusion [8,16]. End-to-end anastomoses can be performed between the donor and recipient external carotid or facial arteries and veins. Once the arterial and venous circulation is restored and the tissue is perfused, the next step is coaptation of facial trigeminal, supraorbital, infraorbital and mental nerves branches.

The entire facial tissue implantation procedure can take between 8 and 16 h to complete. Early complications include graft failure due to vascular thrombosis, infection and acute rejection. In the event of rejection arising from a need to discontinue immunosuppressive medications, the graft can be removed and either a second similar procedure performed at a later date or as an alternative, the surgeon may revert to conventional reconstructive techniques.

4.4. *Functional outcomes*

The first two face transplant recipients have shown a remarkable return of facial function. The first recipient showed near normal sensation of the grafted tissue by 6 months. Motor recovery however was slower with gradual improvement of phonation and mastication and at 18 months she was capable of some facial expressions [18]. The second face transplant recipient from France also showed similar results with early recovery of sensation starting at 3 months post-operatively, with continued improvements noticed at 12 months. In this case however, at the end of the first year, motor innervation was seen predominantly on the left side of the face as compared to the right [9]. This impressive return of function could have been expected based on the previous hand transplantation experience. Hand transplant recipients have shown more than 90% sensory recovery and "satisfactory" motor recovery within 6–12 months post-transplant. All hand recipients were capable of performing normal activities of daily living and patient satisfaction has been reported to be very high [19].

The early functional outcomes in face transplants, confirmed by 10 years of experience in hand transplants, suggests that the surgical/technical aspects of this new reconstructive treatment are sufficiently understood to be able to consistently reproduce good outcomes.

5. Immunological considerations

In this section, we review some key immunological considerations in facial tissue transplantation, beginning with a brief history. While mythology has described transplantation as a cure for disease for many centuries, the modern era of clinical transplantation began in the early 1950s when a team of physicians–scientists led by Joseph Murray transplanted a kidney into a dying, 23-year-old man in the first successful long-term human organ transplant (Table 1) [20,21]. Since then the development of successive new generations of immunosuppressive medications have led to significant reductions in rejection and prolonged organ survival rates as well as reduced drug toxicity. This, in turn has led to the expansion of transplantation to include livers, heart and lung, kidney and pancreas, and small bowel. In spite of this success in solid organ transplantation, tissues that included skin, such as face and hands could not be

infection [35]. In this latter case, biopsy of the transplanted facial tissue did not indicate signs of graft rejection. No deaths have been reported in hand transplant recipients [15].

5.6. Other complications

Hypertension has not been reported in face transplant recipients though it has been reported in 33% of hand transplant recipients [19]. Diabetes has not been reported in face transplant recipients though transient hyperglycemia was observed in 23% of the hand transplant recipients [19]. Ten percent of these also showed elevated serum creatinine levels as did the first face transplant recipient in whom a decreased glomerular filtration rate was reported [18]. In this case the offending drug, tacrolimus, was substituted by sirolimus which caused thrombotic microangiopathy and acute renal failure. This required stoppage of both drugs for a short period followed by a gradual re-introduction of sirolimus [18]. Cushing's syndrome and aseptic necrosis of the hip were other complications reported in hand transplant recipients

preexisting diseases, face and hand transplant recipients are generally healthy. Accordingly the main complications reported in face and hand transplant recipients have been episodes of acute rejection and infection.

5.1. Acute rejection

The first three face transplant recipients from France and the USA all experienced episodes of acute rejection in the first year post-transplant. In all cases these episodes were successfully reversed by adjusting the immunosuppression medications [28,19]. Acute rejection was also reported in hand transplant recipients (85% at 1-year post-transplant) [19,29] which, as in face transplant recipients, was reversed by adjusting the immunosuppression medications. These higher rates of acute rejection, as compared to solid organ transplants, are most likely due to the high antigenicity of the skin [30,31]

key to achieving success in face transplantation. It is essential that candidates be selected based on their ability to understand the risks involved and be compliant with the required life-long

demonstrated repeatedly in all but one Chinese hand and one face transplant recipient whose medication non-compliance has led to graft failure. For further discussions on the psychological aspects of patient selection and compliance, we refer the reader to a separate article on psychological considerations in face transplantation in this issue.

7. Face transplantation for treating severe facial burns

Some of the advantages of face transplantation over conventional treatments for severe facial burns include; improved functional and aesthetic outcomes, fewer numbers of revision surgeries, shorter and more complete rehabilitation, enabling patients to return to work and normal life sooner. The

incidences of acute rejection episodes have been associated with higher rates of chronic rejection [32]. When considering the relatively high incidence of acute rejection observed in face and hand transplant recipients, it is surprising that chronic rejection has not been seen. This low incidence of chronic rejection could be due to several factors: (1) relatively short post-transplant follow-up, (2) low incidence of associated risk factors (hypertension and dyslipidemia) commonly seen in solid organ transplants but not face and hand transplants, (3) a difference in vascular and parenchymal susceptibility to the toxic effects of medications and (4) early identification and reversal of acute rejection in face and hand transplants made possible by the ability to directly view skin rejection and not solid organ rejection [29].

5.4. *Graft loss*

Graft loss (rejection leading to subsequent graft removal) has been reported in 1 of the 7 face transplant recipients, with medication non-compliance being reported as the cause. In this case, after more than 2 years post-transplant, the patient returned to his small town in the countryside in China where he stopped taking his immunosuppression medication. This patient was reported to have died due to complications associated with the rejection of his facial tissue but his family did not allow autopsy and therefore the circumstances surrounding his death are not clear [33,34]. In hand transplant recipients, graft loss has been reported in only one patient from France and all but one of the 11 (8 single hands and 3 bilateral) Chinese patients. In all these cases graft loss occurred due to stopping immunosuppression medications [19].

5.5. *Death*

Two of the 7 face transplant recipients have died, the first in China (described above) and the second, in France. The case in France was reported to have died 2 months after receiving his transplanted facial tissue and bilateral hands due to a cardiac related complication while undergoing surgery to treat infection [35]. In this later case, biopsy of the transplanted facial tissue did not indicate signs of graft rejection. No deaths have been reported in hand transplant recipients [15].

5.6. *Other complications*

Hypertension has not been reported in face transplant recipients though it has been reported in 10% of hand transplant recipients [19]. Diabetes has not been reported in face transplant recipients though transient hyperglycemia was observed in 23% of the hand transplant recipients [19]. Ten percent of these also showed elevated serum creatinine levels as did the first face transplant recipient in whom a decreased glomerular filtration rate was reported [18]. In this case the offending drug, tacrolimus, was substituted by sirolimus which caused thrombotic microangiopathy and acute renal failure. This required stoppage of both drugs for a short period followed by a gradual re-introduction of sirolimus [18]. Cushing's syndrome and aseptic necrosis of the hip were other complications reported in hand transplant recipients but neither complication have not been reported in face transplant patients.

Three years experience with face and 10 years experience with hand transplants has demonstrated that from an immunological standpoint CTA is feasible. In contrast to solid organ transplants the incidence of systemic complications in both face and hand transplants is less. Overall, providing patients are compliant taking their immunosuppression medications, graft survival has been 100% and functional and aesthetic recovery has been described as good.

6. Key considerations for moving face transplant into mainstream medicine

Positive initial outcomes in the first human face transplants have helped transform some of the largely perceived barriers into mere hurdles. The main hurdle continues to be the need to expose recipients to the risks of life-long immunosuppression. As more specific and less toxic methods of manipulating the immune response become available this hurdle will continue to be lowered and thus lead to a greater acceptance of facial tissue transplantation for treating individuals with severe facial disfigurement.

Despite the relative high incidence of acute rejection episodes in these patients, the presently used immunosuppression protocols are effective in preventing rejection in the short and long term. The need to frequently increase the dosages of these medications to prevent rejection episodes has led to over-immunosuppression and increased susceptibility to infection. Chronic rejection and graft failure have occurred less frequently than anticipated.

A major focus of current transplantation research is the development of strategies to induce tolerance thus eliminating the need for toxic immunosuppression medications. Until this quest for the "holy grail" is achieved, the ongoing development of more effective and less toxic drug regimens will continue to push the risk versus benefit balance in favor of face transplantation.

Finally, psychological assessment during patient selection is key to achieving success in face transplantation. It is essential that candidates be selected based on their ability to understand the risks involved and be compliant with the required life-long immunosuppression medications. This requirement has been demonstrated repeatedly in all but one Chinese hand and one face transplant recipient whose medication non-compliance has led to graft failure. For further discussion on the psychological aspects of patient selection and compliance, we refer the reader to a separate article on psychological considerations in face transplantation in this issue.

7. Face transplantation for treating severe facial burns

Some of the advantages of face transplantation over conventional treatments for severe facial burns include; improved functional and aesthetic outcomes, fewer numbers of revision surgeries, shorter and more complete rehabilitation, enabling patients to return to work and normal life sooner. The

disadvantages are primarily associated with the immunotherapy and include episodes of acute rejection and infection. These require close monitoring and can be successfully managed by a change or adjustment in the medications on an out-patient basis.

7.1. *Summary*

At present, patients suffering with severe facial disfigurement due to burn injury are among the most debilitated for whom current treatments do little to improve facial function and appearance. Most often these victims remain isolated and have practically non-existent personal or social relationships. Psychological disturbance, phobias and the requirement of repeated corrective surgeries for progressive deformities make their life miserable. Face transplantation in such patients is a beacon of hope that can offer them a better quality of life.

Facial transplantation is now a clinical reality. The surgical skills necessary to perform face transplantation have been developed over many years and are routinely used in most large facial trauma centers. The immunosuppression medications and protocols used in face transplantation have been developed and perfected over 50 years of clinical solid organ transplantation. The psychosocial and ethical issues associated with face transplantation are being learned in the first cases performed. As additional face transplant procedures are performed and the details responsible for the successes and failures are shared by the teams performing these new reconstructive procedures our gaps in knowledge will be filled.

As solid organ transplantation has saved and improved the lives of so many, so could face transplant improve lives of those suffering with severe facial disfigurement. Of course many hurdles remain, our efforts should focus on finding ways to overcome them, thus assuring that this promising treatment moves into mainstream surgical care for severe facially disfigured patients.

Acknowledgements

The work described here was funded in part by a grant from the Dr. Joseph C. Banis Jr. Research and Education fund in Louisville, Kentucky. Dr. Joseph C. Banis has also contributed in writing this article.

Conflict of interest

There are no financial conflicts of interests between any of the authors listed in this manuscript and the work described in it.

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