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Facial allotransplantation: A 3-year follow-up report



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Summary *Introduction:* Long term follow-up of face transplant patients is fundamental to our understanding of risks and benefits of this procedure. Worldwide experience has shown that function improves gradually over time.

Methods: In April of 2009, a multidisciplinary team at Brigham and Women's Hospital performed face transplantation on a male patient to address a severe facial defect caused by high-voltage burns. Physical and occupational therapy was performed for the first six post-operative months. Close monitoring of the patient's functional recovery, immunosuppression, and quality of life was performed at set time points.

Results: Three years after face transplantation, the patient has recovered near-normal sensation. Along with satisfactory aesthetic results, his motor function continues to improve, aiding his speech, facial expressions, and social interaction. Furthermore, the patient reports continued improvements in quality of life. Infectious, metabolic, and immunologic complications have been successfully managed in a team approach. Immunosuppression doses have been effectively reduced, and steroid therapy was withdrawn before the end of the first post-operative year.

Conclusions: The presented outcomes demonstrate the procedure's growing role in reconstructive surgery as teams continue to focus their efforts on further optimization of immunosuppression and surgical technique.

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Introduction

In the short history of face transplantation (FT), numerous reports on the technical feasibility and early results of the procedure have been published; however, outcome reports beyond 2 years have been rare.¹⁻⁹

Long-term follow-up after face transplantation is paramount, as functional integration of the transplanted facial tissues continues to improve over time, owing to gradual nerve regeneration. At Brigham and Women's Hospital, our technical protocol emphasizes the coaptation of all identifiable motor and sensory nerves as distally as recipient anatomy allows.¹⁰ This technique has resulted in consistent, early return of sensory and motor function in our FT recipients; functional recovery is comparatively diminished in regions not selectively reinnervated.⁵ Conversely, others report near-normal return of sensation in the absence of sensory nerve coaptation.¹¹ In light of these conflicting results, long-term outcome reports may provide further insight into which combinations of surgical technique and physical and occupational therapy regimens may be more effective and/or reproducible.

Another priority is the minimization of the adverse effects associated with immunosuppression. Adverse effects associated with extended exposure to immunosuppressive medications commonly observed in solid organ transplantation have, as of yet, been infrequent in FT recipients. Nonetheless, patients must remain under strict monitoring for long-term toxicity of immunosuppressive drugs.

We present the outcomes of a patient three years after partial face transplantation emphasizing on recovery of sensory and motor functions, immunosuppression and quality of life (QoL).

Methods

Patient JM underwent partial FT in April of 2009 at the Brigham and Women's Hospital (Clinical protocol: 2008P000550, approved by the Partners Human Research Committee). Details of the patient's initial presentation, conventional reconstructive efforts, screening, and surgical technique have been reported previously.¹² Minimal revision procedures, consisting mainly of excision of redundant allograft skin and subcutaneous tissue to improve contour and resting tone have been performed in an ambulatory setting. Other secondary surgeries include the insertion of a Medpor chin implant, extraction of teeth from donor maxilla due to advanced decay, and implant placement in maxilla and mandible for future dental prostheses. A comprehensive review of the patient's medical record identified all complications related to FT as well as details of the immunosuppressive regimen.

Sensory and motor function

To evaluate protective and light sensation, stimulation with Semmes-Weinstein monofilaments was performed on the surface of the allograft and oral mucosa.¹³ To evaluate 2-point discrimination, an aesthesiometer was used to

stimulate the surface of the allograft with the contact points set at 5, 10, and 15 mm apart.¹⁴ Hot and cold sensation was tested on both the surface of the facial allograft and the transplanted oral mucosa.

Physical therapy was initiated the first postoperative week, and continued until postoperative month six, at which point it was discontinued. Voluntary movement of the facial musculature was performed through Manual Muscle Testing.¹⁵ The Motor section of the Sunnybrook Facial Grading Scale was used to further evaluate facial muscle movement and synkinesis.¹⁶

Quality of life and cost data

Facial Disability Index questionnaire was administered at 2, 2.5 and 3-year time points to evaluate the patient's long-term perception of facial functional impairment after FT.¹⁷

Results

Sensory and motor function

Three years after transplantation, the patient has achieved sensation at 0.07 g of pressure in approximately 92% of the allograft's skin and oral mucosa. Sensation to this level of pressure represents "normal sensation".¹³ In the bulb of the nose including bilateral nasal alae, which correlates to approximately 8% of the allograft surface area, the patient reports sensation at 2 g of pressure. This correlates to "diminished protective sensation" (Figure 1).

The patient correctly identifies 2-point stimuli 5 mm and 15 mm apart in approximately 30% and 90%, respectively, of the allograft surface area (Figure 2), indicating near-normal sensory discrimination.¹⁸ The patient has normal thermal sensation in the entire skin surface and oral mucosa of the facial allograft, recognizes the texture of food and correctly identifies when his mouth is empty or full.

When performing Manual Muscle Testing, the patient presents with a functionally intact orbicularis oris and zygomaticus major contraction, bilaterally. Some muscles such as the left levator anguli oris contract weakly. Other muscles have been difficult to identify in contraction, or contraction may be absent (right levator anguli oris, buccinator, levator labii superioris, and levator labii superioris alaeque nasi).

The degree of muscle excursion as measured by the Sunnybrook Facial Grading Scale demonstrated near-normal and close to symmetric movements. The snarl on the right side is rated 1/5, or "Unable to initiate movement". The left side scored 2/5, where the patient "Initiates slight movement". Lip pucker is rated at 3/5, or "Initiated movement with mild excursion" and "Moderate asymmetry".

Complications

Immunologic, infectious, and metabolic complications have been minimal and are summarized in Table 1. Moreover, detailed descriptions of the patient's infectious complications have been recently reported.¹⁹

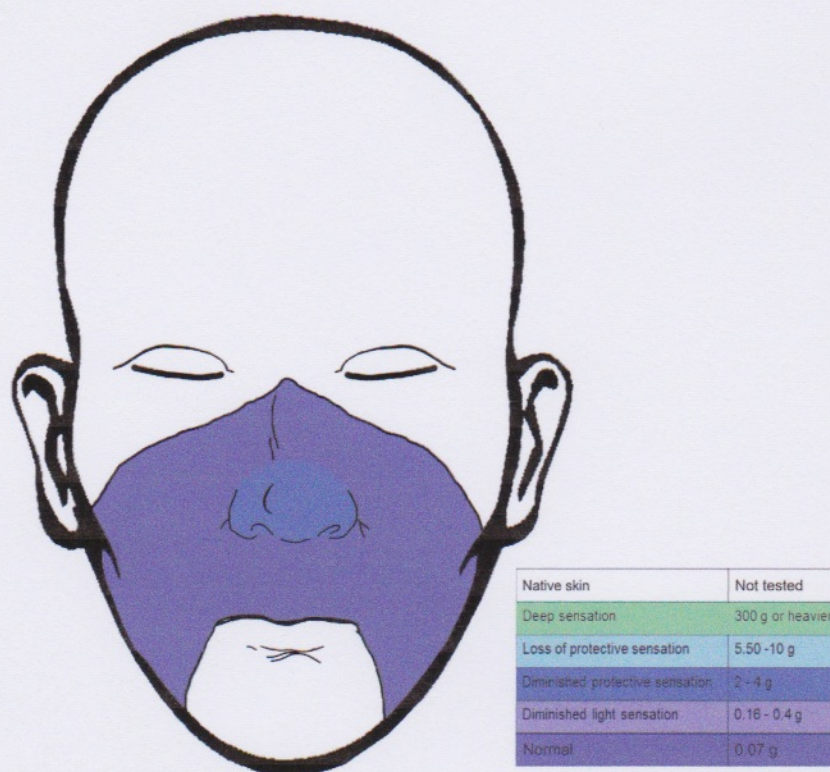


Figure 1 Return of light and protective sensation three years after face transplantation.

Immunosuppression

The patient's current maintenance immunosuppression regimen consists of dual therapy with tacrolimus and mycophenolic acid (Figure 3). Induction treatment with anti-thymocyte globulin (1.5 mg/kg/d \times 4 days) was administered and corticosteroids were withdrawn on day 360. The patient remained on tacrolimus 1 mg bid with trough levels 3–5 ng and mycophenolic acid 180 mg bid. At 2 years and 9 months an acute rejection episode was treated successfully with a temporary increase of maintenance immunosuppression to tacrolimus 2 mg bid (trough levels 8–10 ng) and mycophenolic acid 360 mg bid.

Quality of life

The patient's physical function score at 3 years was 85/100, which represents a steady increase from the 2 and 2.5-year scores of 55/100 and 70/100, respectively. In regards to social wellbeing, the score at 2 years was 88/100. After a decrease to 68/100 at 2.5 years, the patient reported a score of 84/100 3 years after FT.

Discussion

We present long-term outcomes of a patient three years after partial face transplantation to address a severe facial

defect. Facial form, restored immediately after transplantation, continues to improve without requiring major surgical intervention. The allograft has aesthetically integrated into the surrounding native facial skin and lower lip without major differences in color, texture, or contour (Figure 4).

Our program's aforementioned technical approach maximizes the length of native facial nerve fibers in the facial tissues and minimizes synkinesis.¹⁰ Recovery of sensation, like most published cases, began slowly at 3–6 months, and in most areas of the face and oral mucosa is near normal. There has been gradual and progressive improvement throughout, even after discontinuation of physical and occupational therapy. Moreover, there was marked improvement in sensory function from the 2.5-year time point to the three-year mark. This late recovery was unforeseen, and highlights the importance of continuous, long-term postoperative monitoring of FT recipients.

The patient has recovered with an overall considerable motor function. He is orally competent, and he can effectively express himself by complementing his much improved speech with a variety of facial expressions (Video S1). Postoperatively, a strict regimen of physical, occupational, and speech and swallow therapy is critical to the functional recovery of the facial musculature. Involvement of these disciplines in the face transplant patient's care is important, and should begin as early as during the screening phase to increase patient

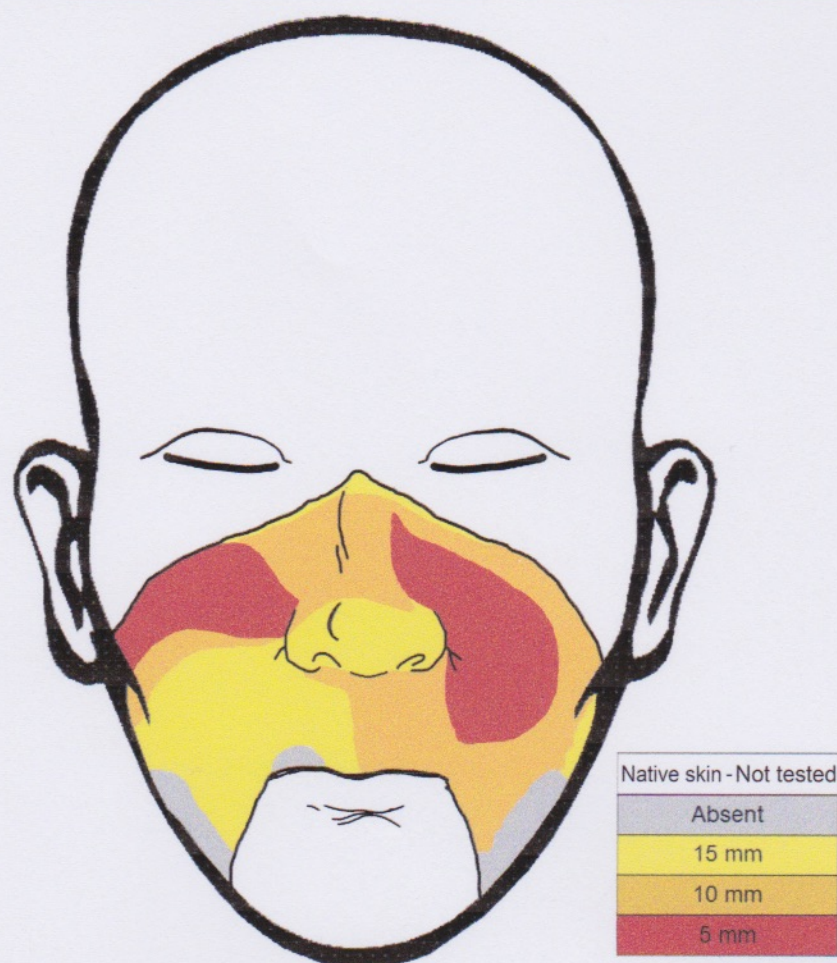


Figure 2 Return of discriminatory sensation three years after face transplantation.

Table 1 Summary of complications after face transplantation.

Time point	Event type	Event	Management
Week 3	Immunologic	Grade I–II acute rejection	Methylprednisolone bolus; 500 mg \times 3
Month 3	Immunologic	Grade I–II acute rejection	Methylprednisolone bolus; 500 mg \times 3
Month 4–6	Immunologic/ infectious	Initial diagnosis: Grade II acute rejection; after persistent erythema and biopsy findings, donor history of Rosacea prompted topical therapy which resolved symptoms	Initial treatment: methylprednisolone bolus; 500 mg \times 3; tacrolimus cream. Treatment for Rosacea: Metronidazole cream 1%
Month 5	Infectious	Left parotitis (not transplanted)	Initial treatment: Vancomycin, Clindamycin, Cefepime. Narrowed to Cefepime alone; 2 g TID
Month 6	Infectious	Subcutaneous dermatophytosis in right foot: Majocchi's granuloma	Terbinafine; 250 mg/day
Month 8	Metabolic	Post transplant type II diabetes mellitus	Insulin; 45 units 75–25/ML am and 30 units 75–25/ML pm
Month 15	Infectious	Cytomegalovirus viremia	Valgancyclovir; 900 mg BID Valgancyclovir prophylaxis; 450 mg bid until month 18
Month 34	Immunologic	Grade 2–3 acute rejection	Increase of maintenance tacrolimus dose (from 0.5 mg BID to 1 mg BID)
Month 35	Infectious	Left parotitis (not transplanted)	Cephalexin; 500 mg QID

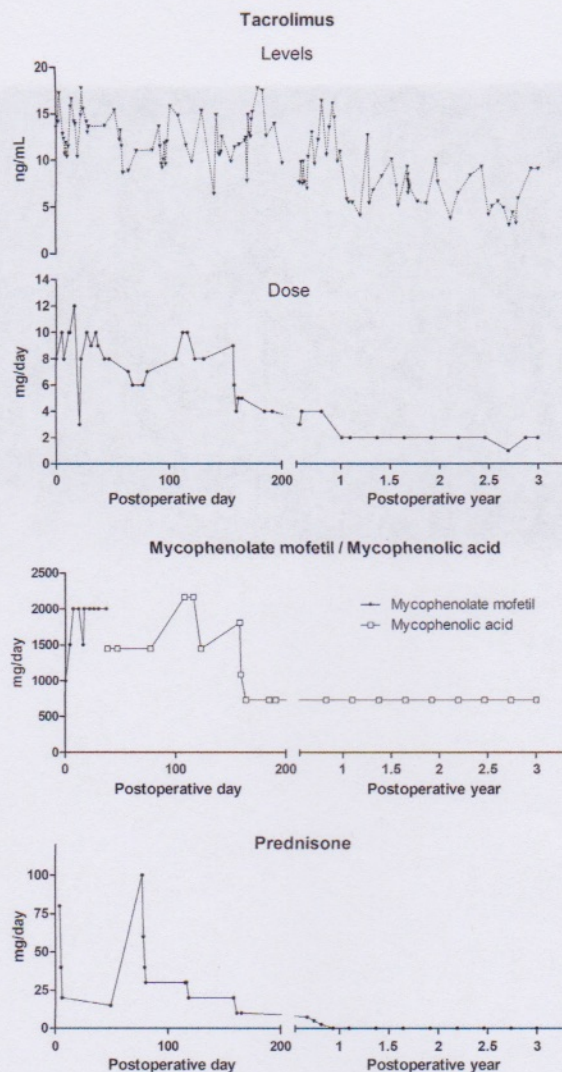


Figure 3 Summary of immunosuppression dosage, tacrolimus trough levels and steroid withdrawal during the first three years post face transplantation.

understanding of the recovery process, and design a therapy program customized to the patient's goals and expectations.

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Of note, validated instruments to measure facial motor function were designed for conditions such as unilateral facial paralysis, and may include comparisons to the unaffected side of the face. Tests designed to measure facial sensation were developed to determine *loss* of sensation, instead of *recovery* of sensation, leading to terminology that does not describe improvement. In addition, reproducibility of results is a concern with current instruments, as sensory and motor testing is highly dependent on patient effort and subjective judgment. Thus, these instruments – even when used in combination – may not adequately capture the variety of factors involved in the functional recovery of this unique population.

The main objective in transplant immunosuppression is to reduce medications to a level that can effectively prevent allograft rejection while avoiding complications such as opportunistic infections. In our patient, most infectious and immunologic events occurred within the first eight months and no significant side effects have been observed long-term.

Post-transplant diabetes mellitus (DM) has been a commonly reported adverse effect of immunosuppression in vascularized composite allotransplantation.²⁰ Our patient had several risk factors and developed DM on postoperative month 8 which has been successfully managed with insulin therapy and lifestyle modifications.

Reports of improved QoL in FT recipients are consistently found in the literature.^{2,5,9} Instruments to objectively measure these variations in patient wellbeing are under development at our institution. In addition, we record QoL data in patients that have undergone conventional reconstructive surgery for comparable facial defects. These data, in combination with a thorough analysis of FT costs, may provide important insight as to the value and cost/benefit profile of FT.



Figure 4 Functional and aesthetic integration of the facial allograft: left: neutral facial expression; center: smiling; right: opening his mouth.

Conclusions

Partial facial transplantation has resulted into an excellent functional and aesthetic outcome demonstrating the feasibility of this procedure for the treatment of large, multi-layer facial tissue defects. The optimization of outcomes relies heavily on a persistent vigilance and involvement of a multidisciplinary team effort. Future efforts will be focusing on an optimization of immunosuppression and a further refinement of surgical techniques.

Conflict of interest statement

The authors have no conflicts to disclose.

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