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Psychological and Psychiatric Aspects of Face Transplantation: Lessons Learned from the Long-Term Follow-Up of Six Patients

Running head: Psychological and psychiatric aspects of face transplantation

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Abstract

Since 2005, at least 38 face transplantations have been performed worldwide. Available recommendations on psychological management are based on isolated cases or small case series, either not focused on mental health or with a short follow-up. We propose herein a clinical commentary on psychological and psychiatric outcomes from the follow-up of a prospective single-center cohort of six patients over a period of 3.5 to 9 years. Seven patients received a face transplant between January 2007 and April 2011: two patients with neurofibromatosis, four with self-inflicted ballistic trauma, one with self-immolation. One patient died at 63 days of cerebral sequelae from cardiac arrest in the setting of bacterial infection. The six other patients were routinely evaluated with unstructured psychological interviews up to May 2016 and with the Short Form 36-item health survey and the Mini-International Neuropsychiatric Interview at one year and at the end of the follow-up. Clinically meaningful observations were the following: a history of mental disorders before disfigurement was associated with poor physical and mental outcomes, including poor adherence and one suicide; untreated depression was associated with poor adherence; acceptance of the new face occurred rapidly and without significant distress in all of the patients; fear of transplant rejection was present to some degree in all of the patients and did not substantially differ from other transplantation settings; media exposure may be disturbing but may also have had positive psychological effects on some of the patients. Mental health issues related to chronic rejection and re-transplantation remain to be explored.

1. Introduction

Since 2005, at least 38 facial vascularized composite allograft transplantations have been performed worldwide (1–3). Overall, the short-term aesthetic, functional, and psychological outcomes reported thus far have been mostly favorable (1–7), whereas early concerns regarding depersonalization and identity confusion with the donors have not been corroborated (3,8). The favorable psychological outcomes include good transplant acceptance and improved body image and social integration (for example, returning to work and resuming social activities), with patients receiving less verbal abuse from others and experiencing fewer depressive symptoms (9). However, short-term decreases in psychological well-being and quality of life have also been reported (9,10). Recommendations about pre-operative and postoperative psychological assessment and management have been issued (11–13). However, most of the present knowledge comes from isolated case reports or small case

series that did not describe a long follow-up (8) or detail mental health issues (5,14). In addition, psychiatric issues such as postoperative delirium or suicidal behaviors have been given less emphasis than psychological issues. The psychological and psychiatric data presented here come from the long follow-up (that is, from 3.5 to 9 years) of six patients included in a single-center, prospective, descriptive study whose main endpoint was the patients' quality of life to determine the benefit/risk ratio of face transplantation. This study has been described elsewhere but without focus on the psychological or psychiatric aspects (5). Regarding the psychological aspects, the potential impact of depressive symptoms, fear of rejection, or media exposure on adherence and quality of life has not been described and patients' acceptance of their new face has not been discussed further. Regarding the psychiatric aspects, the high rate of postoperative delirium was not mentioned and the suicide of one patient was only briefly noted. The aim of this report was to refine our knowledge regarding the psychological and psychiatric aspects of face transplantation by providing an extended clinical commentary on important mental health issues that have been overlooked or only briefly mentioned in the previous general report (5).

2. Brief overview of the study

Between January 2000 and December 2009, 20 patients presenting with non-reconstructable facial defects and severe functional disabilities related to tumors, burns, and ballistic trauma were assessed for eligibility (5). The main exclusion criteria were a recent history of cancer and unstable psychiatric conditions. The final decision for inclusion in the study required a multidisciplinary unanimous approval (15,16). All of the included patients provided written informed consent after (i) full information, (ii) several months of follow-up evaluations (regarding both physical and mental health) to confirm the absence of exclusion criteria, and (iii) repeated evaluations of the individual benefit/risk ratio with the participation of the patient.

Ten patients were considered eligible for facial transplantation due to their facial defects and related functional disabilities: two patients with neurofibromatosis 1 (patients #1 and #5); four patients with ballistic trauma (patients #2, #4, #6, and #7), three patients with burn injury (patients #3, #8, and #10), and one patient with xeroderma pigmentosum (patient #9). Three of these patients were finally not included: two burn patients presenting with broad and intense anti-HLA sensitization, and the patient with xeroderma pigmentosum, who developed a poor prognosis melanoma. The patients who survived self-inflicted ballistic trauma (patients #2, #4, #6, and #7) or self-immolation (patient #3) were considered stable following repeated psychiatric evaluations. Two (patients #2 and #6) had no history of mental disorder and

consistently claimed their traumas were accidental. These patients subsequently presented with depressive episodes requiring antidepressant medication but achieved sustained, full remission at the time of face transplantation. The three other patients had a history of bipolar II disorder (patient #3), recurrent depressive disorder and substance use disorder (patient #4) and alcohol use disorder with a comorbid depressive episode at the time of suicide attempt and a first-degree family history of suicide attempts (patient #7).

Seven patients thus received a face transplant between January 21, 2007, and April 16, 2011. Post-transplantation rehabilitation included speech therapy, range-of-motion exercises, and sensory re-education. Although patient #3 was included in the original study, he will not be presented here as he died 63 days post-transplantation of cerebral sequelae from cardiac arrest in the setting of bacterial infection. The six patients whose data are presented here were routinely evaluated with unstructured psychological interviews up to May 2016 as well as with the Short Form 36-item health survey and the Mini-International Neuropsychiatric Interview (17) after one year and during the last year of the follow-up. In addition, they underwent functional assessment by physical and speech therapists and video recording and sensory tests. Patient #7 died by suicide 3.5 years post-transplantation (see below).

This study was conducted according to the guidelines published by the French national ethics committee (notice number 82, February 6, 2004, “L’allotransplantation de tissu composite (ATC) au niveau de la face: Greffe totale ou partielle d’un visage” and its subsequent amendments). All of the patients provided written informed consent for the use of their clinical data for up to 5 years of follow-up at the time of their inclusion. With the exception of patients #3 and #7, who died during follow-up, all of the subjects renewed their consent for the period lasting from their inclusion to the end of the study (May 15, 2016) as authorized by the ethics committee, resulting in a follow-up duration of 3.5 to 9 years (5).

3. Clinical histories of the six patients with long-term follow-up

The clinical history of each patient has been detailed elsewhere (5). This report focuses on the functional and psychosocial outcomes up to the end of the study. Figure 1, adapted from (5), displays the SF-36 physical and mental component scores at inclusion, at one year, and at the last available evaluation together with the main patients’ characteristics, including their psychological and psychiatric features. Figure 2 displays the eight SF-36 subscales at inclusion, at one year, and at the last available evaluation.

3.1. Patient #1

Patient #1 was a 29-year-old man suffering from neurofibromatosis 1 that led to 16 facial surgical procedures since childhood. Face transplantation was the only viable surgical option

to restore labial competence and allow normal speech and feeding. At the time of the psychological and psychiatric assessment, he was living with his mother and was increasingly concerned by his persistent unemployment after a long period of regular employment as an accountant. He reported ruminative thoughts during adolescence regarding his appearance and its social consequences but had no personal history of mental disorders. He displayed efficient coping strategies and had strong family support. Six months after inclusion, he received a lower two-thirds facial transplant on January 21, 2007 (15).

During the first two days post-transplantation, the patient experienced moderate to severe symptoms of postoperative delirium that warranted the transient use of sedative drugs. During the first week, the patient could see his new face with a positive psychological impact. He was able to speak and eat by day 10 and displayed spontaneous mimicry at 9 months. Although no compliance problems have been reported, he had the highest number of rejection episodes, with a first episode at day 28 revealed by mild erythema. The transplant function remained unaltered. Hypertension was detected and treated 7.5 years after transplantation.

Patient #1 experienced substantial improvement in his quality of life after the transplantation (Figure 1). Improvement in social functioning took place progressively during the first year (Figure 2). Initial concerns about the way others would react to his new appearance, especially his mother, progressively vanished. At 13 months, he found full-time employment and maintained it up to the end of the study. He was able to carry out activities of daily living unassisted, including being well understood in a face-to-face interview and on the phone and eating normally. Despite the repeated episodes of rejection, he experienced only rare and transient periods of anxiety and remained optimistic about long-term outcomes, with no psychiatric events reported at the end of the study (that is, 9 years of follow-up).

3.2. Patient #2

Patient #2 was a 26-year-old Spanish man who survived a self-inflicted ballistic trauma in 2005. He was engaged to a young woman but eventually ended their relationship after the injury. Despite 13 reconstructive procedures, his speech remained barely intelligible, he had no labial competence, and he required a tracheostomy and permanent jejunostomy. Despite high levels of impulsivity, he did not meet the diagnostic criteria for a specific personality disorder and had no personal history of mental disorders before the trauma. Indeed, he consistently claimed the ballistic trauma was accidental and his relatives did not suggest that it could have been a suicide attempt. His mother presented with a history of suicide attempts. He experienced a major depressive episode with suicidal ideation in the months following the trauma, for which he required a short hospitalization in Spain, received antidepressant drugs

(escitalopram, mirtazapine, and clomipramine) together with benzodiazepines, and subsequently received local psychiatric follow-up. At inclusion, he was in remission under clomipramine 75 mg per day and was well supported by his family. He was also receiving valproic acid to decrease impulsivity with no evidence of bipolar disorder. Six months after inclusion, he remained in remission when he received a lower two-thirds facial transplant on March 23, 2009.

At day 2 post-transplantation, he experienced mild symptoms of postoperative delirium that warranted the transient use of sedative drugs. During the first week, he could see his new face. He recovered intelligible speech at day 10, regained the ability to eat at day 24, and was discharged at day 60. Living abroad, he was followed in collaboration with a local team. He faced the lowest number of rejection episodes, with only one episode requiring treatment at one year. He nonetheless developed hypertension. He showed fast motor recovery with complete mouth closure at about 8 months. His speech was then easily understandable in a face-to-face interview and by phone and he could eat by mouth with a close to normal diet.

At 6 months post-transplantation, in a context of financial difficulties at his father's company and another suicide attempt by his mother, he experienced a depressive episode that warranted a switch from clomipramine to venlafaxine and weekly supportive psychotherapy. Although he again achieved full remission, he subsequently presented with several yet more transient relapses but continued to be compliant with immunosuppressant therapy. He resumed part-time work at his family enterprise at one year post-transplantation. Despite no substantial improvement in his mental health quality of life, his overall quality of life increased and remained good at a 6-year follow-up (Figure 1).

3.3. Patient #4

Patient #4 was a 33-year-old man who survived a self-inflicted gunshot injury in 2005. The patient acknowledged suicidal intent and a psychiatric assessment revealed that he was suffering from a recurrent major depressive disorder with comorbid alcohol and cannabis use disorders. The suicide attempt occurred in the context of marital separation and financial problems. He had two young children and worked as a lumberjack. He underwent 11 reconstruction attempts over two years and required a permanent tracheostomy. During this period, his depressive symptoms required paroxetine treatment. He subsequently achieved satisfactory remission and suffered no addiction relapse. When evaluated for the transplantation three years after the trauma, the patient was psychologically stable, compliant to medication, motivated for the transplantation, and well supported by his family, especially

his mother and his sister. Six months after inclusion, he received a lower two-thirds facial transplant on August 18, 2009.

In the immediate aftermath of the transplantation, he experienced mild symptoms of postoperative delirium that warranted the transient use of sedative drugs. During the first week, he could see his new face at day 8 with a positive psychological impact. The feeding tube was removed at day 21. The patient recovered intelligible speech at day 24 and was discharged at day 73. The absence of motor recovery on the right side after 11 months led to a revision procedure for coaptation of the facial nerve that allowed mouth closure after 8 to 12 months. The patient could then eat a normal diet by mouth and be well understood in a face-to-face interview and by phone.

The patient seemed to adapt quite well to the situation during the first 6 months after transplantation, with only transient concerns regarding the anticipated reaction of his children to his new appearance and impatience and irritability related to a feeling of confinement at the end of the initial hospitalization. At 6 months post-transplantation, however, he presented with significant depressive symptoms with anxiety and impulsivity. He also reported being increasingly concerned with other people's stares, to a greater extent than before the transplantation. Unfortunately, the patient became reluctant to pursue further psychological and psychiatric care and follow-up. He went back to work as a lumberjack but his quality of life did not improve, especially because of poor mental health (Figure 2). He presented with multiple acute rejection episodes associated with poor medication compliance in relation to his depressive symptoms. During the following years, the patient became increasingly non-compliant, resumed alcohol and tobacco consumption, and then presented with rejection episodes of increasing severity requiring intense immunosuppressant therapy to prevent transplant loss.

3.4. Patient #5

Patient #5 was a 35-year-old man suffering from severe sporadic neurofibromatosis 1 that led to 15 facial surgical procedures since childhood. A right eye glaucoma led to enucleation. At the time of the psychiatric and psychological assessment, he was living alone, working as a theatrical technician, and was well supported by his relatives. He reported a history of treatment by fluvoxamine for transient symptoms of anxiety, without meeting the criteria for any diagnosis of present or past mental disorders. He nonetheless reported long-lasting distress regarding other people's staring and mocking and had important aesthetic expectations. On June 27, 2010, he received the first full-face transplant worldwide.

During the first week post-transplantation, he could see his new face with an immediate sense of ownership and positive psychological outcomes. The feeding tube was removed at day 12 and the tracheostomy at day 17 and the patient was discharged at day 38. The first clinical signs of motor recovery appeared at 6-9 months post-transplantation. At 2.5 years post-transplantation, he suffered an iatrogenic acute kidney failure requiring a drastic reduction in his immunosuppressive regimen. He subsequently developed grade 3 rejection that was successfully treated with a steroid bolus. His renal function partially recovered after 6 months but he had moderate renal insufficiency with hypertension at the end of the study.

The patient returned to part-time employment at day 190. However, his steroid-associated muscle fatigue led him to quit his physically demanding work and undergo a professional conversion to a librarian. He could be well understood in a face-to-face interview and by phone and could eat a normal diet by mouth. His mental health quality of life improved due to good social outcomes, but some gains had been lost at the last follow-up (5 years) due to difficulties in finding stable work. However, he remained euthymic throughout the follow-up, displaying the necessary psychological resources to cope with social and physical difficulties. For instance, the kidney failure episode resulted in only moderate and transient increased anxiety and did not lead to enduring psychological distress. At the end of the study, a skin biopsy revealed chronic rejection leading to partial necrosis of the graft. Although the patient transiently displayed anxiety and depressive mood, he did not meet the criteria for a depressive episode or even adjustment disorder due to adaptive coping strategies.

3.5. Patient #6

Patient #6 was a 49-year-old man who survived a self-inflicted ballistic trauma in 2009. At the time of trauma, he was living with his wife and two children, aged 12 and 17, and working as fisherman. He had no personal history of mental disorder and consistently claimed that the gunshot was accidental. His wife and relatives did not provide any evidence suggesting suicidal intent. Considering the facial defect and the 3-year outcomes of the first face transplantation, the patient was directly referred for face transplantation after the stabilization of the jaw remnants. He also suffered from a visual impairment secondary to damage to the right optic nerve. He required a permanent tracheostomy and a feeding tube. His expectations regarding the graft were mainly functional: being able to speak and eat again. He was enrolled five months after the trauma. At the time of pre-transplantation assessment, a depressive episode was diagnosed. He received psychological support and escitalopram 10 mg per day and had achieved full remission when he received a lower two-thirds facial transplant on May 12, 2011.

In the immediate aftermath of the transplantation, the patient experienced moderate symptoms of postoperative delirium that warranted the transient use of sedative drugs. He underwent several revision procedures but only one episode of rejection at two months. Moderate iatrogenic renal failure was detected a few months afterward and persisted through the last follow-up.

At the end of the study, the patient remained unemployed and dependent on others, especially his spouse and his mother, for everyday life because of visual impairment and major speech limitations caused by tongue alteration. Despite these difficulties and the development of renal failure, he remained euthymic and optimistic about his future, allowing antidepressants to be stopped, and was fully compliant with immunosuppressant therapy.

3.6. Patient #7

Patient #7 was a 48-year old man who survived a self-inflicted ballistic trauma in 2005. Over 3 years, he underwent 28 reconstructive procedures that failed to provide a functional mouth and a socially acceptable face. The psychiatric assessment revealed a history of alcohol use disorder with a first-degree family history of alcohol use disorder and suicide attempts. He had no personal history of mood disorder but this first suicide attempt occurred during a first major depressive episode in the context of a divorce and financial difficulties. The patient was enrolled 4.5 years after the trauma. At the time of inclusion, he was euthymic and well-motivated. He was maintaining relationships with his two children, aged 14 and 25, and had a new romantic relationship. Although he lived in a rural area and no longer worked, he was socially integrated despite his disfigurement. He received a lower two-thirds graft on April 16, 2011.

The patient required a prolonged hospitalization from 100 to 200 days post-transplantation because of CMV infection and subsequently developed iatrogenic renal insufficiency.

Despite satisfactory aesthetic and functional outcomes, patient #7 was the only subject to have a reduced quality of life at one year. This decrease was mainly driven by the physical component (Figure 1), but the mental component also remained affected following his prolonged hospitalization during which he expressed feelings of boredom and exhibited fluctuating anxiety and increasing irritability, but without a characterized psychiatric episode. He suffered from a second major depressive episode at 17 months post-transplantation and stopped the immunosuppressant therapy for 15 days. This depressive episode was successfully treated and he reported no suicidal ideation. No rejection episode was detected at a maximal follow-up of 3.4 years. Because of tongue damage, he had persistent speech limitations and remained unemployed. Although he did not experience formal depressive

relapse and benefitted from strong family support, he committed suicide by hanging himself at 3.5 years in a context of financial problems. Neither his relatives nor his caregivers anticipated this suicide.

4. Lessons from the long-term follow-up of the six patients

4.1. Adapting to a new face

As recommended (11–13), progressive yet early exposure of the patient to their new appearance in the mirror, as well as engaging in self-care activities, was encouraged and did not yield significant distress in any of the patients. We did not observe excessive avoidance or scrutiny. Consistent with other groups, we also did not observe symptoms of depersonalization or feelings of donor identity transfer or split (3).

Some points should be highlighted. First, the superficial characteristics of the donor combined with the bone architecture of the recipient's face so that the recipient's new face was merely a new face. Second, for the six patients, face transplantation took place long after the disfigurement, so most had already experienced the loss of their native face for years. Third, all of the patients but one (patient #6) underwent several reconstructive surgical procedures before face transplantation so they had experienced repeated changes in their face over a long period of time. This might have allowed them to dissociate their sense of identity from their appearance. Fourth, repeated psychiatric and psychological assessments before transplantation might have prepared the patients for this new change in appearance. To the best of our knowledge, only one case of immediate face transplantation has been published thus far, so the importance of such preparation cannot yet be ascertained (18).

Gradual yet early social exposure was also encouraged. Overall, the six patients displayed greater anxiety regarding exposure to relatives, progressively replaced by anxiety regarding exposure to strangers, especially for the two patients with neurofibromatosis 1. Psychological distress regarding other people's stares decreased in all but one patient (patient #4).

In their spontaneous comments, the patients did not avoid nor focus on the topic of their new appearance. All of the patients eventually considered their graft as their own face, reflecting their personality and emotions. This integration process was probably supported by the overall satisfactory functional outcomes, especially the early recovery of sensitive feedback, as described by those who have undergone hand transplantation (19). This is consistent with the idea that body ownership is a dynamic phenomenon that remains active throughout life. Patient #1 deserves to be quoted here. He reported that he realized that his new face had become more familiar than his native face when he saw an old video of himself talking. Static pictures of his native face did not previously have the same effect. It seems that the

confrontation with the dynamic representation of both his old and new faces through video and mirror respectively helped him accept his new face.

Finally, the belief that “deformation will not occur any longer,” explicitly stated by the two patients with neurofibromatosis, might have further promoted the acceptance of their new face.

4.2. Fear of transplant rejection

Fear of rejection is an important psychological issue for patients with transplanted organs. All of the patients in this study had episodes of acute cell-mediated rejection with grade above 2 between 30 days and 7 years after transplantation. It has been suggested that fear of rejection after face or hand transplantation might differ from that observed after solid organ transplantation, as the signs of rejection can be observed by the patients (13). This long-term follow-up study showed that early detection of rejection relied primarily on clinical examination in the first year only. After one year, acute rejection episodes could be clinically silent or present with non-classical signs such as lichenoid patches or erosions (5). In accordance, no evidence was found that fear of rejection was substantially different in patients with face transplantation compared to those with solid organ transplantation (for example, increased anxiety due to anticipation of the results of systematic biopsy).

4.3. Mental disorders and mental health quality of life

All of the patients but one experienced mild to severe symptoms of postoperative delirium in the immediate aftermath of the transplantation. This high rate, which may be explained by several risk factors (for example, the duration of the procedure and/or the use of high dosages of steroids), might require pre-operative information of the patient and his or her relatives and particular attention from the clinicians to prevent early complications (for example, poor compliance with invasive care in the intensive care unit). Symptoms of postoperative delirium were easily managed with sedatives and antipsychotic drugs. There was no evidence that immunosuppressant therapy could account for significant psychiatric outcomes other than early postoperative delirium.

Among the four patients with self-inflicted trauma who survived at long-term follow-up, the two with an established history of mental disorders before the trauma had poor psychiatric outcomes. Although patient #4 was euthymic and abstinent at the time of face transplantation, he had a history of recurrent major depressive disorder with comorbid alcohol and substance use disorder. After the transplantation, he experienced a relapse of both disorders that compromised his immunosuppressant therapy compliance and quality of life and for which he refused further psychiatric assistance. This resulted in repeated and severe rejection episodes.

Patient #7, who had a history of alcohol use disorder and was depressed at the time of his suicide attempt, experienced a major depressive episode at 17 months post-transplantation, with a transient lack of immunosuppressant therapy compliance. Although he fully remitted under antidepressant treatment, he eventually died by suicide, hanging himself at 3.5 years post-transplantation. Overall, these two patients did not seem to have experienced substantial improvements in their quality of life after face transplantation (Figure 1).

This is in contrast to patients #2 and #6 who both claimed that the self-inflicted ballistic trauma was an accident during skeet shooting and hunting activities, respectively. This was corroborated by the patients' relatives, whereas none directly witnessed the accidents. This was also consistent with the lack of an established history of mental disorders for both patients. Although these two patients experienced post-disfigurement depressive episodes, it did not result in poor adherence to either immunosuppressant therapy or psychiatric care. Furthermore, patient #6 did not experience post-transplantation depressive relapse and showed dramatic and sustained improvement in his mental health quality of life, without psychotropic medications, despite relatively stable physical health quality of life, unemployment, impaired vision, and compromised autonomy (Figure 1).

Finally, the two patients with neurofibromatosis had no history of mental disorders before transplantation and did not develop depressive episodes afterward. Instead, both experienced substantial and sustained improvements in their mental health quality of life (Figure 1), especially regarding social functioning (Figure 2).

Overall, poor psychiatric outcomes after transplantation seemed to be mainly predicted by a history of mental disorders before disfigurement.

4.4. Medical adherence

Poor adherence to immunosuppressant therapy after face transplantation has been reported to account for multiple episodes of rejection and ultimately death (3). Although impulsivity may confound the association between suicide attempt and poor medical adherence (20), the present study instead emphasizes the potential role of a concomitant depressive episode in the two patients who presented with poor medical adherence after transplantation. For patient #4, the rebuttal of further psychological and psychiatric care was associated with persistent poor adherence and multiple acute rejection episodes of increasing severity. For patient #7, the effective management of depression with supportive psychotherapy and antidepressant drugs resulted in restored compliance to immunosuppressant therapy, preventing rejection. This is consistent with the literature showing an association between depression and poor medical

adherence in various settings, including solid organ transplantation (21–23). In addition, randomized controlled trials suggest that treating depression could improve adherence (24).

4.5. The role of the media

The role of the media in potentially disturbing patients and their relatives, as well as the donor's relatives and health care providers, has been anticipated early (12). Patients should be provided with appropriate counseling regarding media exposure and preventing unwanted media intrusion. Less emphasis has been put on potentially positive influences. The experience of both patients with neurofibromatosis might mitigate these media-related concerns. Patient #1 gave interviews and described how media coverage helped him feel accepted again. Such positive influence was even greater for patient #5, who benefitted from the first full face transplantation worldwide. Media exposure not only helped him restore a positive image of himself, but eventually combined with patient #5's personal long-lasting inclination toward books and literature, leading him to write a book about his life.

5. Conclusion

The aim of this report was to increase our knowledge regarding the psychological and psychiatric aspects of face transplantation by providing an extended clinical commentary on data gathered from six patients followed over 3.5 to 9 years. These observations should be interpreted with caution due to several limitations. First, the small sample size obviously calls into question the generalizability of our conclusions and prevents statistical analysis of the quantitative data collected. Second, quality of life was quantitatively measured at only three time points and there is a lack of quantitative data regarding important psychological areas such as body image or fear of rejection. Third, the psychological interviews on which this report was mainly based were not structured and were not scheduled at a regular pace, depending on the visits of the patient for other clinical purposes. A formal qualitative analysis was therefore not carried out. In addition, patient #4 became reluctant to undergo psychological and psychiatric assessments after one year of follow-up so that qualitative data are lacking afterward. Fourth, although the diagnosis of mental disorders at inclusion was based on the Mini-International Neuropsychiatric Interview (17), this structured clinical interview was only used twice during the follow-up. Future studies should combine long-term monitoring with the systematic collection of quantitative and qualitative data.

Despite these limitations, some lessons may be learned from this prospective cohort of six patients. First, a history of mental disorders before disfigurement, as found in the two patients with self-inflicted ballistic trauma with acknowledged suicidal intent, was associated with

poor physical and mental outcomes, including poor adherence and suicide. Second, untreated current depression was associated with poor adherence. Third, the integration of the new face into the patients' body image occurred rapidly and without significant distress, even in the patients with a history of mental disorders. Fourth, fear of transplant rejection was present to some degree in all of the patients and did not seem to substantially differ from other transplantation settings, although this was not quantified by a specific psychometric assessment. Fifth, although media exposure may be disturbing, it can also have positive psychological effects on some patients.

The present report suggests that the prolonged remission of mental disorders at the time of transplantation might not be sufficiently stringent as inclusion criteria to prevent poor outcomes. Since patients with self-inflicted ballistic trauma represent the archetype of face transplant candidates due to their anatomical lesions and functional impairment, considering the exclusion of patients who were disfigured after a suicide attempt would substantially reduce the number of potential recipients. To date, patients with self-inflicted ballistic trauma and burns comprise two-thirds of all transplant recipients worldwide (3). However, the present report suggests considering as potential exclusion criteria a history of mental disorders that preceded disfigurement rather than self-inflicted trauma per se, as suggested by the satisfactory outcomes of patients #2 and #6. In contrast, patients #4 and #7 did not seem to have experienced substantial improvements in their quality of life after face transplantation (Figure 1). Since face transplantation is supposed to be life-enhancing rather than life-saving, and because there are no organ shortages in face transplantation, such exclusion criteria might not raise the same ethical issues than in life-saving solid organ transplantation.

The fact that patients #2 and #6 and their relatives claimed that the self-inflicted ballistic traumas were accidental may elicit several interpretations. First, although the injuries were prototypical of those observed after a suicide attempt, they might nonetheless have been accidents, consistent with the lack of reported psychiatric history or stressful life events in both cases. Second, denial may have occurred as a way to cope with extreme stress at both the individual and collective levels. Third, the patients and their relatives may have been prone to voluntarily presenting a suicide attempt as an accident for social desirability reasons, including a perceived increase in the likelihood of being eligible for transplantation. Although social desirability may bias psychological and psychiatric assessments toward overoptimistic conclusions, it may also signal stronger patient motivation. Against the social desirability hypothesis, however, both patients #2 and #6 readily disclosed their depressive symptoms at the pre-operative assessment.

The death of patient #7 by suicide deserves some specific comments. One may wonder whether face transplantation was causally involved to some extent. No evidence was found to support this hypothesis. First, a history of a suicide attempt by firearm is in itself a strong risk factor for subsequent suicide (26). Second, although the patient's quality of life did not improve from inclusion, it did not deteriorate either (Figure 1), suggesting that his suicidal ideation was unrelated to the transplantation functional outcomes. Third, the context in which he committed suicide was similar to the one in which he first attempted suicide (that is, financial difficulties), suggesting that such a context might have played a more important role than the medical context. As previously mentioned, this event was unanticipated by both his relatives and his caregivers. Patient #7 did not present with depressive symptoms during the 3-month hospitalization in the first year post-transplantation, nor with suicidal ideation during the depressive episode at 17 months. His suicide attempt might nonetheless have been facilitated by a recent, undiagnosed relapse of depressive or alcohol use disorder.

In conclusion, the present report suggests that face transplantation may not be life-enhancing in candidates with self-inflicted trauma and a history of mood or alcohol use disorder before disfigurement. Future retrospective and prospective studies should determine whether self-inflicted disfigurement with ascertained suicidal intent should constitute potential exclusion criteria, even in the absence of any identified mental disorder. Several other questions remain to be explored, including the effects of face transplantation on other functional domains, such as sexuality or emotion recognition (27), as well as psychological challenges related to chronic rejection and eventual re-transplantation (1,28).

References

1. Siemionow M. The miracle of face transplantation after 10 years. Br Med Bull. 2016;120(1):5□14.
2. Lassus P, Lindford A, Vuola J, Bäck L, Suominen S, Mesimäki K, et al. The Helsinki Face Transplantation: Surgical aspects and 1-year outcome. J Plast Reconstr Aesthetic Surg JPRAS. 2018;71(2):132□9.
3. Khalifian S, Brazio PS, Mohan R, Shaffer C, Brandacher G, Barth RN, et al. Facial transplantation: the first 9 years. Lancet. 2014;384(9960):2153□63.
4. Dubernard J-M, Lengelé B, Morelon E, Testelin S, Badet L, Moure C, et al. Outcomes 18 months after the first human partial face transplantation. N Engl J Med. 2007;357(24):2451□60.

5. Lantieri L, Grimbert P, Ortonne N, Suberbielle C, Bories D, Cebrián SG-V, et al. Face transplant: long-term follow-up and results of a prospective open study. Lancet. 2016;388(10052):1398-1407.
6. Gordon CR, Siemionow M, Papay F, Pryor L, Gatherwright J, Kodish E, et al. The world's experience with facial transplantation: what have we learned thus far? Ann Plast Surg. 2009;63(5):572□8.
7. Guo S, Han Y, Zhang X, Lu B, Yi C, Zhang H, et al. Human facial allotransplantation: a 2-year follow-up study. Lancet. 2008;372(9639):631□8.
8. Pomahac B, Pribaz J, Eriksson E, Bueno EM, Diaz-Siso JR, Rybicki FJ, et al. Three patients with full facial transplantation. N Engl J Med. 2012;366(8):715□22.
9. Coffman KL, Siemionow MZ. Face transplantation: psychological outcomes at three-year follow-up. Psychosomatics. 2013;54(4):372□8.
10. Chang G, Pomahac B. Psychosocial changes 6 months after face transplantation. Psychosomatics. 2013;54(4):367□71.
11. Coffman KL. Psychiatric evaluation of the face transplant candidate. Curr Opin Organ Transplant. 2015;20(2):222□8.
12. Morris P, Bradley A, Doyal L, Earley M, Hagen P, Milling M, et al. Face transplantation: a review of the technical, immunological, psychological and clinical issues with recommendations for good practice. Transplantation. 2007;83(2):109□28.
13. Brill SE, Clarke A, Veale DM, Butler PEM. Psychological management and body image issues in facial transplantation. Body Image. 2006;3(1):1□15.
14. Kollar B, Pomahac B. Facial restoration by transplantation. Surgeon. 2018;16(4):245-249.
15. Lantieri L, Meningaud J-P, Grimbert P, Bellivier F, Lefaucheur J-P, Ortonne N, 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(9639):639□45.
16. Lantieri L, Hivelin M, Audard V, Benjoar MD, Meningaud JP, Bellivier F, et al. Feasibility, reproducibility, risks and benefits of face transplantation: a prospective study of outcomes. Am J Transplant. 2011;11(2):367□78.
17. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;quiz 34-57.

18. Maciejewski A, Krakowczyk Ł, Szymczyk C, Wierzgoń J, Grajek M, Dobrut M, et al. The First Immediate Face Transplant in the World. Ann Surg. 2016;263(3):e36-39.
19. Vargas CD, Aballéa A, Rodrigues EC, Reilly KT, Mercier C, Petruzzo P, et al. Re-emergence of hand-muscle representations in human motor cortex after hand allograft. Proc Natl Acad Sci U S A. 2009;106(17):7197□202.
20. Lebeau G, Consoli SM, Le Bouc R, Sola-Gazagnes A, Hartemann A, Simon D, et al. Delay discounting of gains and losses, glycemic control and therapeutic adherence in type 2 diabetes. Behav Processes. 2016;132:42□8.
21. Lin C, Clark R, Tu P, Bosworth HB, Zullig LL. Breast cancer oral anti-cancer medication adherence: a systematic review of psychosocial motivators and barriers. Breast Cancer Res Treat. 2017;165(2):247□60.
22. Chilcot J, Spencer BWJ, Maple H, Mamode N. Depression and kidney transplantation. Transplantation. 2014;97(7):717□21.
23. Crawshaw J, Auyeung V, Norton S, Weinman J. Identifying psychosocial predictors of medication non-adherence following acute coronary syndrome: A systematic review and meta-analysis. J Psychosom Res. 2016;90:10□32.
24. Tsai AC, Weiser SD, Petersen ML, Ragland K, Kushel MB, Bangsberg DR. A marginal structural model to estimate the causal effect of antidepressant medication treatment on viral suppression among homeless and marginally housed persons with HIV. Arch Gen Psychiatry. 2010;67(12):1282□90.
25. Folkman S. The case for positive emotions in the stress process. Anxiety Stress Coping. 2008;21(1):3□14.
26. Runeson B, Tidemalm D, Dahlin M, Lichtenstein P, Långström N. Method of attempted suicide as predictor of subsequent successful suicide: national long term cohort study. BMJ. 2010;341:c3222.
27. Lisan Q, George N, Hans S, Laccourreye O, Lemogne C. Postsurgical Disfigurement Influences Disgust Recognition: A Case-Control Study. Psychosomatics. 2018;59(2):177□85.
28. Lantieri L, Grimbert P, Ortonne N, Lemogne C, Wolkenstein P, Hivelin M. Facial transplantation: facing the limits, planning the future. Lancet 2017;389(10076):1293□4.

Figure legends

Figure 1. Quality of life (SF-36 norm-based physical and mental component scores) at inclusion, at 1-year post-transplantation, and at maximal follow-up and the main characteristics of the six patients with long-term follow-up adapted from (5).

The bottom panel displays the main characteristics of the six patients in the following order: demographics and social support at the time of inclusion, psychological features and history of mental disorders before disfigurement (for the patients disfigured by a gunshot), occurrence of mental disorders after disfigurement, occurrence of mental disorders after transplantation, employment status, and other comorbid conditions at the end of follow-up.

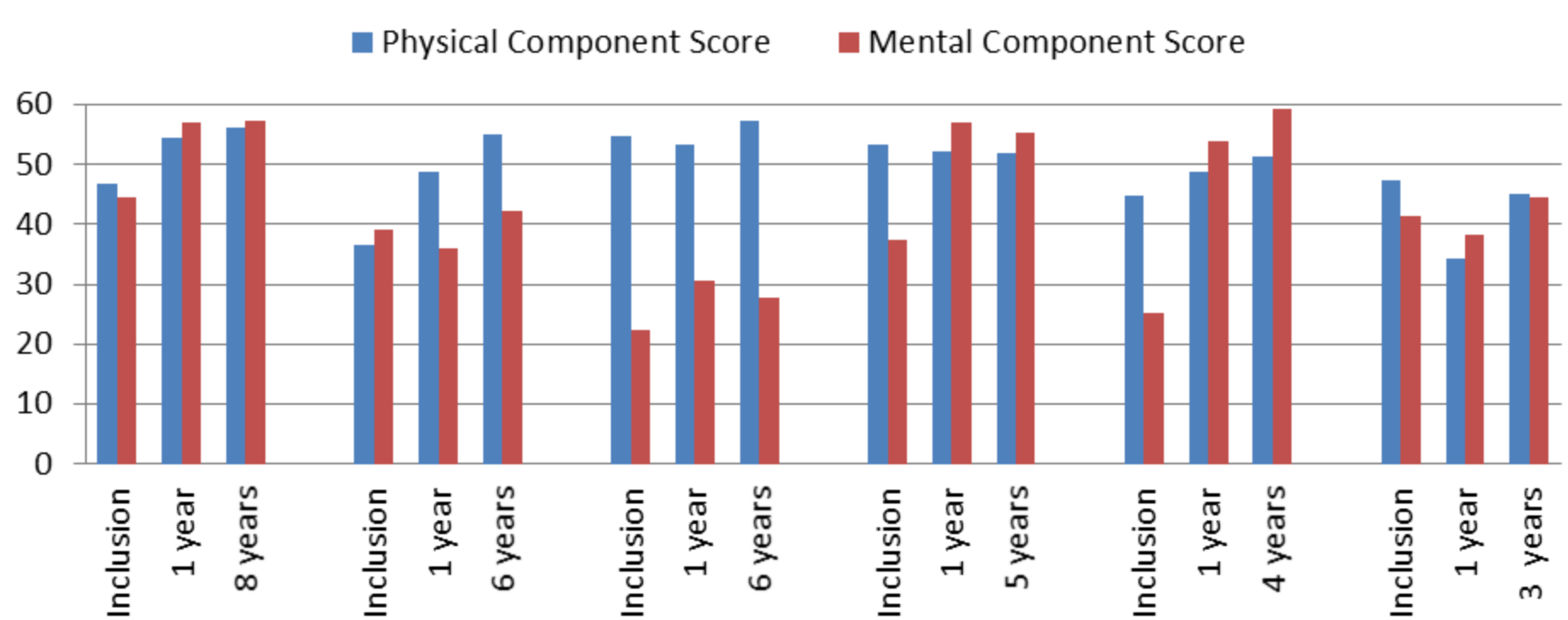
Alcohol UD: alcohol use disorder; MDD: major depressive disorder; MDE: major depressive episode; NF1: neurofibromatosis 1; Post-disfig.: post-disfigurement; Post-transpl.: post-transplantation; Substance UD: substance use disorder.

The green/red line surrounding the patient number indicates overall favorable/unfavorable psychological or psychiatric outcomes.

Figure 2. Quality of life (SF-36 norm-based subscales) at inclusion, at 1-year post-transplantation, and at maximal follow-up.

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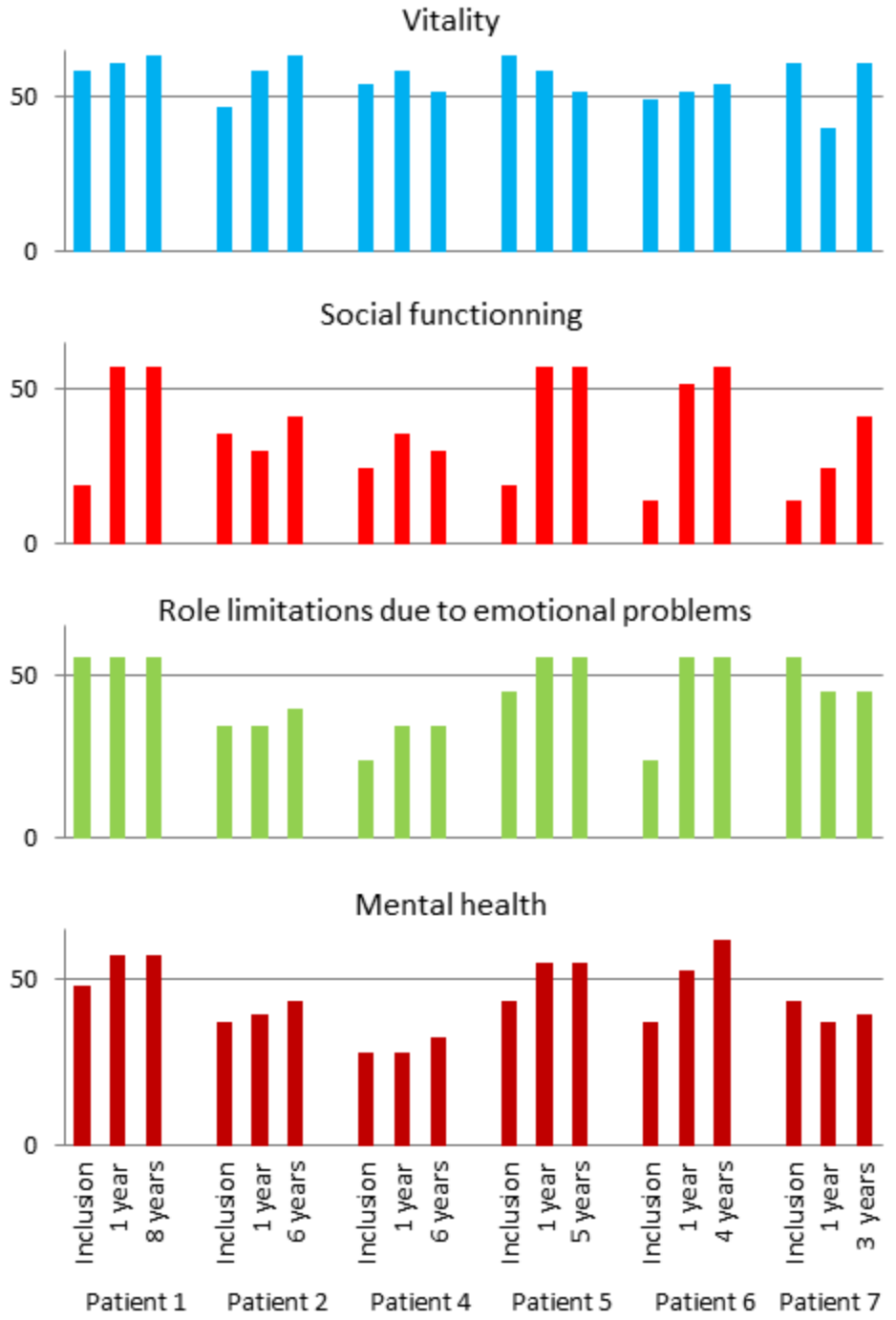
Patient #1	Patient #2	Patient #4	Patient #5	Patient #6	Patient #7
29-year-old man	26-year-old man	33 year-old man	35-year-old man	49-year-old man	48-year-old man
Living with his mother, not working, strong social support	Living alone, not working, good social support	Separated, financial problems, not working, poor social support	Living alone, working, strong social support	Living with his wife, not working, strong social support	Divorced, financial problems, poor social support
No psychiatric history	Impulsive traits	Substance UD Recurrent MDD	Subclinical anxiety		Alcohol UD MDE
NF1	Gunshot (accident?)	Gunshot	NF1	Gunshot (accident?)	Gunshot
Concerned with his unemployment	Post-disfig. MDE with suicidal ideation	Post-disfig. MDE		Post-disfig. MDE	
Postoperative delirium	Postoperative delirium	Postoperative delirium		Postoperative delirium	Post-transpl. MDE
	Post-transpl. MDE	Post-transpl. MDE			
Resumed work	Resumed work	Resumed work	Resumed work	Still unemployed	Still unemployed
Hypertension	Hypertension	**Poor compliance**, severe rejection episodes	Renal insufficiency, hypertension	Renal insufficiency	Renal insufficiency **Suicide**


Physical functionning
50
0
Inclusion
1 year
8 years
Inclusion
1 year
6 years
Inclusion
1 year
6 years
Inclusion
1 year
5 years
Inclusion
1 year
4 years
Inclusion
1 year
3 years
Patient 1
Patient 2
Patient 4
Patient 5
Patient 6
Patient 7

Role limitations due to physical problems
50
0

Bodily pain
50
0

General health perception
50
0


Vitality
50
0
Inclusion
1 year
8 years
Inclusion
1 year
6 years
Inclusion
1 year
6 years
Inclusion
1 year
5 years
Inclusion
1 year
4 years
Inclusion
1 year
3 years
Patient 1
Patient 2
Patient 4
Patient 5
Patient 6
Patient 7

Social functionning
50
0

Role limitations due to emotional problems
50
0

Mental health
50
0