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Face graft? Extrapolation of facial allotransplantation to children

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ABSTRACT

The possibility to imagine a vascularized composite allotransplantation for disfigured children is felt more critical than for adults non on technical point of view but in terms of indications and justifications. The question is not about surgery. It is related to the pathologies themselves for which transplant could be suitable. Moreover the procurement of face transplant will be more difficult because of immunologic criteria but also age and phototype. Specificity of the newborn malformative face is usually not only a question of tissue defect. It is reasonably not an indication for VCA. It should be added that nothing is known about the future of transplantation in terms of duration but also morbidities due to immunosuppression. Indications are rather negative.

To rise the question of VCA for children has a double benefit. The first is to point out that surgical innovation often arise from a non imaginable or non imagined clinical situation. The second is the question of VCA in newborn regarding the tolerance.

"In each case we find ourselves in the presence of a man of genius who began by making great discoveries, and then asked himself how one would have to go about it to make them: a course paradoxical to all appearances and yet the only natural one, since the opposite method of procedure had been tried much more frequently and had never succeeded."

(Bergson, 1969)

1. Introduction

Can composite tissue allotransplantation of the face be considered as an option in children? And, if so, what unknown factors have yet to be resolved? Moreover, is this question really relevant, inasmuch as history has shown that, in the field of surgery, circumstances and actions have always preceded theoretical concepts? Finally, can the limited experience acquired in adults be extrapolated to children?

These are some of the questions that the surgeon who performed the first face transplantation nine years ago (Devauchelle et al., 2006) and who is now extending these techniques to disfiguring congenital malformations would like to share with the reader, even if not all of these questions can be answered at the present time. The term "face graft", although held in contempt by the French National Ethics Advisory Committee (National Official Journal, 2002), was deliberately chosen for the title of this article, as it reflects the ontological dimension of this type of surgical procedure.

2. Facial allotransplantation

Use of the term "composite tissue allotransplantation" of the face is based on more than two hundred scientific papers published in the literature before the procedure had even been performed, together with several hundred articles published in the specialist press since. This fastidious review of the literature suggests that, as in other disciplines, the spoken and written word prevails over acts.

As the term "face graft" speaks for itself, performing, showing, hearing about and seeing this procedure are sufficient to justify the use of this term rather than a tedious discussion of its meaning. However, exhibitions require catalogues and explanations, and "medical science" feeds on figures and words.

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One of the most recent review articles on facial transplantation (Khalifian et al., 2014) illustrates the limitations of this exercise, that of a retrospective view that is designed to be objective and comprehensive. This review was based on 28 cases of "face graft" performed over a nine-year period, although our own review identified 31 cases (Table 1) with no written record of seven of the cases reported in the previous review.

However, a strong point of this publication was that this author had personally performed one face graft (March 2012) and conducted a rigorous critical analysis. Another strong point is that this article highlighted the essential aspects of tolerance and immunosuppressive therapy, functional rehabilitation and especially neurological rehabilitation, spatialization of the facial skeleton and restoration of dental occlusion, with a briefer discussion of

Table 1
Worldwide distribution of allotransplantations (2005–2013).

Patient	Date	Place	Surgical team	Age Gender	Etiology
1	November 2005	Amiens **France**	Devauchelle Dubernard	38/F	Dog bite
2	April 2006	Xi'an **China**	Guo	30/M	Bear bite
3	January 2007	Paris **France**	Lantieri	29/M	Neurofibromatosis
4	December 2008	Cleveland **USA**	Siemionow	45/F	Gunshot wound
5	March 2009	Paris **France**	Lantieri	27/M	Gunshot wound
6	April 2009	Paris **France**	Lantieri	37/M	Third-degree burn
7	April 2009	Boston **USA**	Pomahac	60/M	Electrical burn
8	August 2009	Paris **France**	Lantieri	33/M	Gunshot wound
9	August 2009	Valencia **Spain**	Cavadas	42/M	Cancer sequelae
10	November 2009	Amiens **France**	Devauchelle Dubernard	27/M	Gunshot wound
11	January 2010	Seville **Spain**	Gomez-Cia	35/M	Neurofibromatosis
12	March 2010	Barcelona **Spain**	Barrett	30/M	Gunshot wound
13	June 2010	Paris **France**	Lantieri	35/M	Neurofibromatosis
14	March 2011	Boston **USA**	Pomahac	25/M	Electrical burn
15	April 2011	Paris **France**	Lantieri	45/M	Gunshot wound
16	April 2011	Paris **France**	Lantieri	41/M	Gunshot wound
17	April 2011	Boston **USA**	Pomahac	30/M	Electrical burn
18	May 2011	Boston **USA**	Pomahac	57/F	Animal attack
19	January 2012	Ghent **Belgium**	Blondeel	M	Industrial accident
20	January 2012	Antalya **Turkey**	Ozkan	45/M	Burn
21	February 2012	Ankara **Turkey**	Nasir	25/M	Burn
22	March 2012	Ankara **Turkey**	Ozmen	20/F	Gunshot wound
23	March 2012	Baltimore **USA**	Rodriguez	37/M	Gunshot wound
24	May 2012	Antalya **Turkey**	Ozkan	34/M	Burn
25	June 2012	Amiens **France**	Devauchelle Dubernard	52/F	Vascular tumor
26	February 2013	Boston **USA**	Pomahac	44/F	Chemical burn
27	May 2013	Gliwice **Poland**	Maciejewski	33/M	Gunshot wound
28	July 2013	Antalya **Turkey**	Ozkan	27/M	Gunshot wound
29	August 2013	Antalya **Turkey**	Ozkan	54/M	Gunshot wound
30	December 2013	Gliwice **Poland**	Maciejewski	26/M	Neurofibromatosis
31	December 2013	Antalya **Turkey**	Ozkan	22	Gunshot wound

psychological and ethical issues and, from this last point of view, emphasizing the cost of such an operation.

Whether an error of the time, or a result of submission or attraction to “biopower”, the author concluded by calling for definition of a protocol for the procedure and its indications, although the first lesson to be drawn from facial allotransplantation is that it is unique and performed for the first time in each patient.

A more unfortunate aspect is that these same scientific journals accept to publish the opinions of experts who have only an outsider's view, censors claiming detachment, who are all the more peremptory in their aphorisms the further they are removed from the subject (Smeets et al., 2014).

We will therefore not adopt the description of a surgical procedure that needs to be reinvented each time and the reader is invited to critically review these articles.

3. Possibility of facial allotransplantation in children

This possibility will be discussed humbly and with clear awareness (as the author of these lines may one day need to renounce them) from a surgical point of view (technique – indications).

Technically, there is no difference between face graft for an acquired defect (traumatic or following tumor resection) in adults or children. Anatomical structures are certainly smaller in children, but their physiological capacities remain intact and tissue regeneration and healing are more rapid. In the case of a congenital malformation syndrome (assuming that it requires such treatment), it must first be ensured that distant blood vessels and nerves correspond to classic anatomy. In other words, there are barely any surgical differences between replantation and transplantation.

3.1. Indications

Assuming that transplantation of all or part of the face is possible in children, is it nevertheless indicated?

3.1.1. Facial burns

Facial transplantation was initiated and then justified in the context of treatment of the sequelae of burns. Paradoxically, only four cases of facial transplantation have been performed for burns in adults, although the three cases performed in Boston (two electrical burns and one chemical burn) should also be added to the total. One of these cases died from infectious complications and only limited data are available concerning the medium-term outcome of the three Turkish cases.

Possibly as a result of an error of logic, facial allotransplantation was initially proposed for this indication, by highlighting its ideal “resurfacing” aspects, while underplaying the expected functional benefit. Conceptually, we still have no results concerning restoration of facial expressions in this indication: do platysma muscles need to be transplanted? Should they be superimposed? And how can they be reinnervated?

There are probably a few isolated cases of very severe sequelae of facial burns in children. Apart from one South American case (Fig. 1), the authors have never reported facial transplantation for this indication. The same questions as those raised in adults will apply if ever such a procedure is required.

3.1.2. Traumatisms

Although the rule of thirds (forehead, nasomaxillary, mandibular) applies to the adult face, the same does not apply to very young infants, in whom the face is divided horizontally into two equivalent halves (fronto-cranial and naso-orbito-maxillo-mandibular), which exposes the infant's face to a lower risk of trauma and gunshot wounds in children are almost non-existent in peace time.

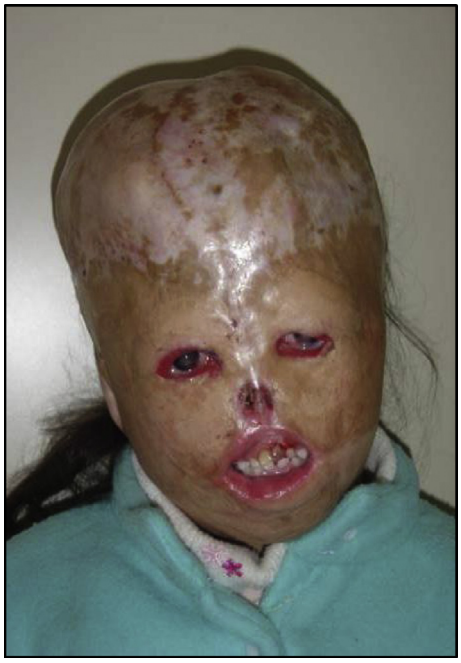


Fig. 1. Fourteen-year-old patient: sequelae of panfacial burns at the age of 2 years.

However, a child's face is particularly vulnerable to animal bites, which often lacerate but rarely amputate the face, except possibly for the external ear. An original case of reimplantation of a largely amputated face is reported in the literature with an excellent long-term result, as the fragment was not excessively lacerated. This particular clinical setting, as in our original case in an adult, was certainly most suitable for possible transplantation of the missing part and these same anatomical zones (the perilabial circle in this case) constitute the best indication for this procedure. We have reported a case of labio-mandibular amputation that was repaired by a prefabricated gracilis free flap transfer. The result may be subject to criticism and raises the question of the possible impact of scar retraction on mandibular growth (Lengele et al., 2014).

3.1.3. Malformations

The intimate organo-genetic dependence between the face and the brain makes agenesis of all or part of the face a nonviable malformation. There is no facial counterpart to anencephaly. Although, from this point of view, nature abhors monsters, to use Canguilhem's expression (Canguilhem, 1966), mythology has extensively developed on what is observed in nature (Cyclops and Janus) and teratology has filled innumerable formalin jars, many craniofacial malformations remain viable, for which complex repair procedures have been developed over the years, but which nevertheless leave severe morphological and functional sequelae in adulthood. As a result of antenatal diagnosis, these malformations are now observed less and less frequently in France.

Many classifications have been proposed for these malformations (Stricker et al., 1990), but two main types can be distinguished:

- Cleft malformations: classified by Paul TESSIER (Rougier et al., 1977), they are not so much due to a defect (agenesis) as to dysraphia or incomplete formation (dysplasia), allowing the surgeon to perform reconstructions using the subject's own tissues, without necessarily requiring auto- or allotransplantation.

A recent doctorate thesis (Racz, 2014) reviewed the rarer forms of these anomalies, and reported no new case since 2005. The illustration (Fig. 2) presented here concerns an Algerian infant.

- "Neoplastic" malformations: this term is used by analogy, as although teratoma is a true benign tumor, its neonatal expression results in a malformation (and teratoma has a very specific meaning). The essential question raised by a teratoma is whether it is compatible with life when the tumor obstructs the upper aerodigestive tract. Even in the presence of a giant teratoma (foetus-in-foetu), simple resection at the time of birth leaves the infant with only moderate sequelae.
- Vascular malformations are somewhat different. Although hemangioma is an authentic tumor that can now be treated medically, lymphatic, venous or arteriovenous malformations can be very extensive and resection of these malformations will require reconstructions that are so complex that allotransplantation may need to be considered. However, the natural history of these malformations is capricious and poorly controlled. Consequently, in order to avoid the mutilation that would inevitably be induced by extensive surgical resection, therapeutic trials currently focus on the use of medications, sclerosis, interventional radiology or destruction by new forms of energy (high frequency, laser, etc.). Nevertheless, these diseases progress uncontrollably over time, are not amenable to etiological treatments (a treatment that would redirect morphogenesis), and can only be treated by palliative measures. This results in an impotent compromise: a dilemma between radical surgery to eradicate the malformation, which would be life-threatening, but which may improve quality of life and a contemplative, compassionate but impotent attitude.

3.1.4. Tumors

Neonatal facial tumors are extremely rare. Several sarcomas have been reported, such as the example shown in Fig. 3. This case was life-threatening and this poor prognosis justified a bolder surgical approach and therefore a more severe mutilation. However, allotransplantation, the procedure most likely to be able to restore form and function, is virtually impossible whenever the repair process comprises immunosuppressive therapy. Immunosuppressive therapy can lead to reactivation of the tumor that has been eradicated from the body, as the body retains a memory of the tumor and the slightest impairment of immune defences allows the tumor to recur. What is true in children is also true in adults.

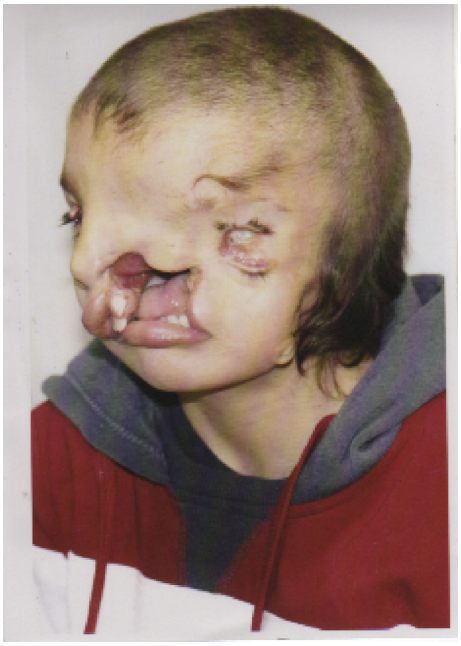


Fig. 2. Nine-year-old Algerian child with multiple, complex facial clefts.

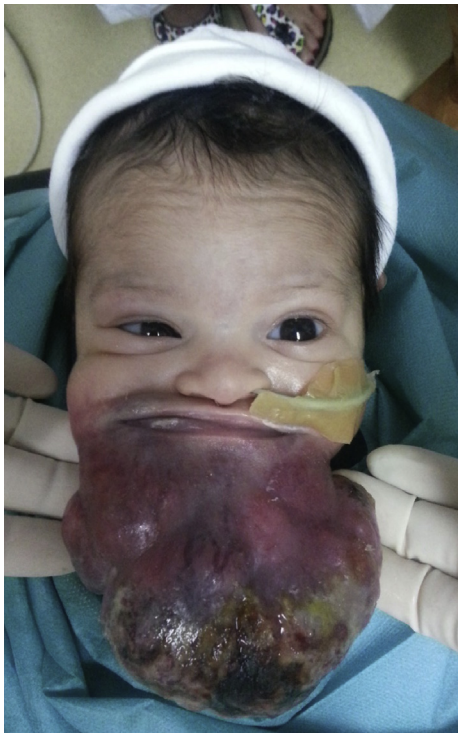


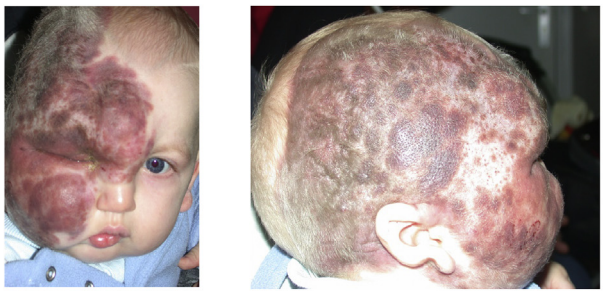
Fig. 3. Child with a rhabdoid tumor (appearance at one week of life).

Neonatal benign tumors are also exceptional, for example, hemangioma, the extent of which can be life-threatening: medical treatment has modified the outcome of such tumors.

A single personal case of congenital nevus of the hemiface, illustrated in Fig. 4, raised the question of a possible indication for transplantation. The extent and depth of this giant hamartoma were responsible for uncontrollable functional (ocular) and painful (pruritus) consequences. Independently of the risk of malignant transformation, the relative urgency to resolve the problem led us to prefer an intermediate solution, which, several years later, proved to be the right choice, although the result failed to achieve the initial objectives. This case illustrates the problem of possible growth of a transplant and the geography of transplantation inevitably requiring left profile – right profile comparison, resulting in what can be called a "schizophrenic" face.

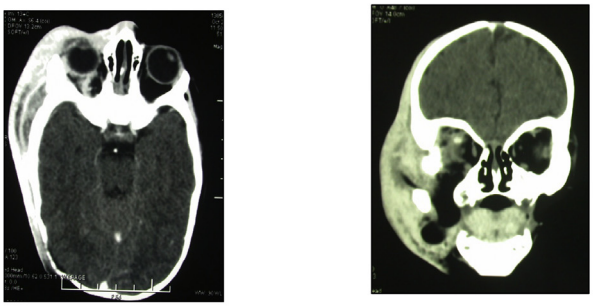
Von Recklinghausen disease (neurofibromatosis type 1) corresponds to a very different situation with progression during growth resembling that observed in certain venous or lymphatic vascular malformations. No data are available concerning the impact of partial surgery on the course of this disease. The four cases of facial allotransplantation in adults in this indication suggest that, as a result of incomplete resection, the treatments performed before and after transplantation have very little impact on progression of the disease.

A single case of Von Recklinghausen disease, followed for almost twenty years since early childhood, that ended dramatically with the indication for hemifacial transplantation, would strongly support earlier more radical surgical management, or, on the contrary,



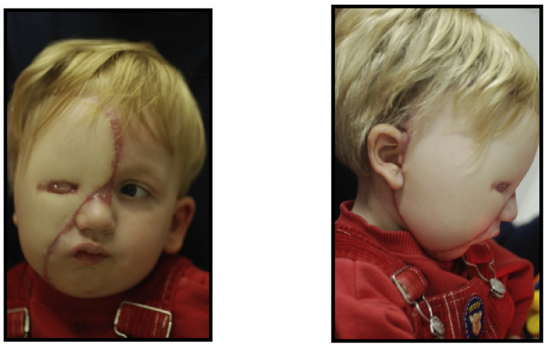
A B

Patient at the age of 10 months (A-B)



C D

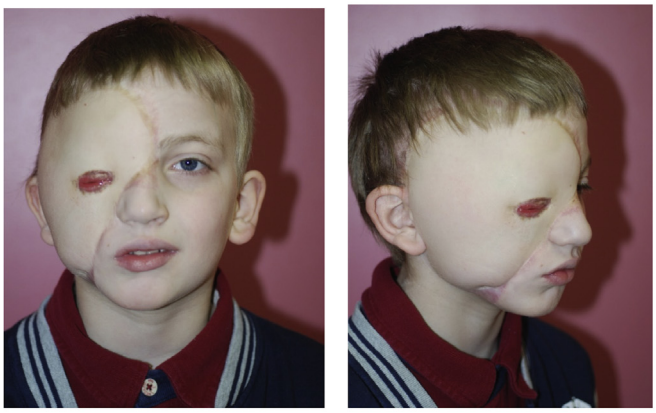
Axial and coronal CT scans (C-D)



E F

Eczematization and limitation of mouth opening, constituting an indication for wide resection and cover by latissimus dorsi free flap. Preservation of the right eye and tarsal conjunctiva.

Result at the age of three years (E-F)



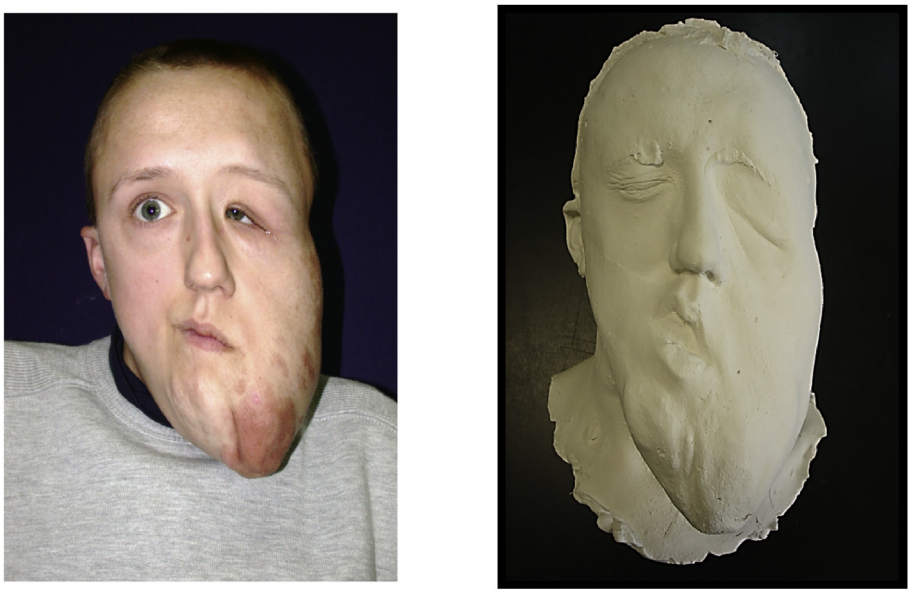
G H

Appearance at the age of 10 years (G-H)

Fig. 4. Congenital hemifacial giant nevus with deep infiltration (A–H).

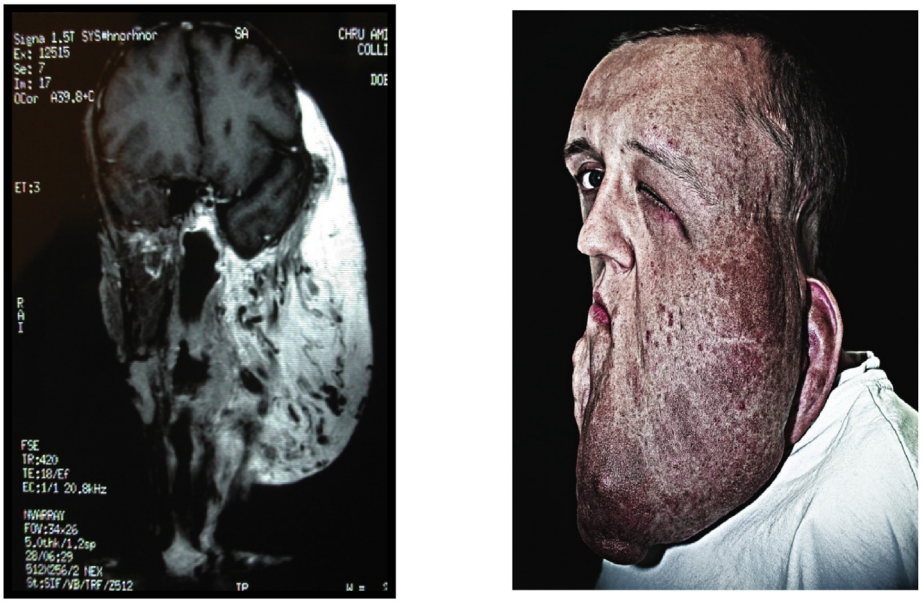
watchful waiting when no other treatment option is available. This case once again illustrates the need for humility (Fig. 5).

It would be impossible, here, to list all of the neonatal or infantile diseases involving the face which, because of their severity or their extent, could possibly constitute future indications for face transplantation. The authors' clinical experience must inevitably be compared with that of other pediatric specialists and is simply presented here as a non-comprehensive illustration. Consequently, independently of each surgeon's clinical practice, the indication for facial transplantation in children will be determined less by surgeons than by the unexpected nature of the disease with which they are faced.



A B

Appearance at the age of 11 years (A-B)



C D

Progressive deformity during growth (C: coronal CT scan)

Appearance at the age of 20 years (D)

Fig. 5. Patient followed for Von Recklinghausen disease since childhood (A–D) (Exclusive facial lesion).

3.2. Growth

Although the growth of an individual is classically related to dietary, hormonal and hereditary factors, less is known about the growth of a transplanted organ. Should growth be considered to be anisotropic in one situation and isotropic in the other? Can organ transplantation be so easily extrapolated to composite tissue allotransplantation? Moreover, skeletal growth of facial bones is known to be partly related to the biomechanical loads exerted on these tissues, as form and function are intimately related.

As there are virtually no data on this subject in the literature, can the findings observed in adults or in autologous face transplantation in children be extrapolated to composite tissue allotransplantation?

- *Allotransplantation in adults*

Due to either a lack of objective measurements or insufficient follow-up, no obvious change in the volume of face transplants has been observed in adults. At most, the "autonomic" functions of skin transplants can be considered to be entirely restored (body hair, vasodilatation or vasoconstriction, pigmentation, etc.). Repeated rejections, as in our second case of face transplantation, certainly lead to tissue sclerosis and retraction. As pioneers in this field, this was our subjective impression concerning our first patient, but transplant function (movements) can be considered to be decreased due to a certain degree of muscle atrophy.

In the present case, concerning what can be called the fourth dimension, i.e. time, we were more particularly interested in aging of the transplant. The present interpretation is somewhat contradictory and partial, as although the skin of the transplant appears to age less rapidly, with a smoother appearance and fewer wrinkles, can this be attributed to decreased mechanical loading by facial expressions, although a certain degree of atrophy would lead to a more rapidly aging appearance?

- *Autologous transplantation in children*

Although we have no personal experience of autologous transplantation of a toe to reconstruct thumb aplasia, which could constitute a useful paragon, we can report a case of fibula transplantation for replacement of a hemi-mandible with a follow-up of several years. In a child operated for mandibular sarcoma, growth of the lower third of the face presented no signs of marked asymmetry. However, although the fibula continued to grow in its longitudinal axis, the bone did not appear to have thickened, leaving a narrow bone graft. It can be argued that, in this case, a bone with membranous growth was replaced by a bone with enchondral growth, and that the fibula is not sensitive to the biomechanical loadings related to mouth opening and closing movements and it is also not submitted to the pressures exerted during mastication due to the absence of teeth. However, in contrast, it must be remembered that the growth of long bones in terms of volume and not in terms of length is dependent on the pressures exerted on the bone (Fig. 6).

In any case, there is every reason to believe that face allotransplantation in children would obey the rules of nature provided the age difference between the donor and the recipient is as small as possible, which inevitably raises the question of the possibility of organ donation.

3.3. Organ donation

The shortage of organ donations constitutes a real obstacle to organ transplantations, as organ needs in France are covered in only one in three cases. To varying degrees, this obstacle, related to cultural and religious aspects, is the same or even more marked in other countries. This reality, which cannot be subject to any judgment, is even more critical when looking for a donor for all or part of the face. Would we even dare ask ourselves this question, not so much as a potential donor, but as parent of a brain-dead child? How can we dare delegate this request to transplant coordination teams, composed of young mothers, especially as some of these teams are not even willing to ask adults to donate a cornea or a part of the face needed by a recipient? The waiting time in this particular context was several months for each of our three cases of adult face transplantation. Would this waiting time be compatible with progression of the disease (when this is the case) in pediatric recipients?

The question raised in the title of this paper, conveniently answered by a discussion of the techniques, raises two other critical questions concerning supply and demand in this cruel metaphorical setting which uses market terms with all of their inhumanity, when the very subject concerns the basis of our humanity*.

* "*You surgeons require both a great deal of humanity and a great deal of inhumanity*" (Valery, 1938)

4. Benchmarking

We probably needed a meeting of pediatric surgeons to finally discuss, for the first time (thereby filling a gap in the literature, except for a recent publication (Doumit et al., 2014) on this subject), facial transplantation in children. We have only been asked on one occasion by faciomaxillary surgeons at Necker children's hospital to contribute to the debate by the French Academy of Surgery.

Before definitively closing this debate, the ramifications of which will only be finally clarified by clinical observation, it may be useful to review the past to see whether similar questions were raised in the context of other composite tissue allotransplantations.

More generally, the recent publication by DOUMIT concluded that it is currently premature to consider composite tissue allotransplantation in children, whether for reconstruction of the extremities or the face, due to the complications of immunosuppressive therapy and the unknown effects in terms of growth. However, this publication was only based on a review of the literature.

A more interesting approach is that adopted by BERLI (Berli et al., 2013) concerning the repair of large defects of the abdominal wall associated with underlying organ transplantation. Based on a review of the abundant literature (more than 280 articles), they identified five studies and compared two different technical approaches. One quarter of these 17 cases were children under the age of 15 years. Only six of these 17 cases were still alive, without complications, with a follow-up ranging from two to seven years. The authors did not find any publication specifically devoted to abdominal wall reconstruction. Like other authors, they concluded that composite tissue allotransplantation can only be indicated, at the present time, for multi-organ transplantations and only after progress has been made in terms of tolerance and therefore in terms of immunosuppressive therapy.

Just as the hand preceded the face in the history of transplantation, it also precedes the face in this hypothesis of neonatal allotransplantation. Two articles published by the same authors (Gazarian and Abrahamyan, 2007; Solla et al., 2013) immediately reached the same conclusions: until the immunological issues have been resolved, allotransplantation cannot be considered for reconstruction of aplasia of a distal part of the upper limb. However,

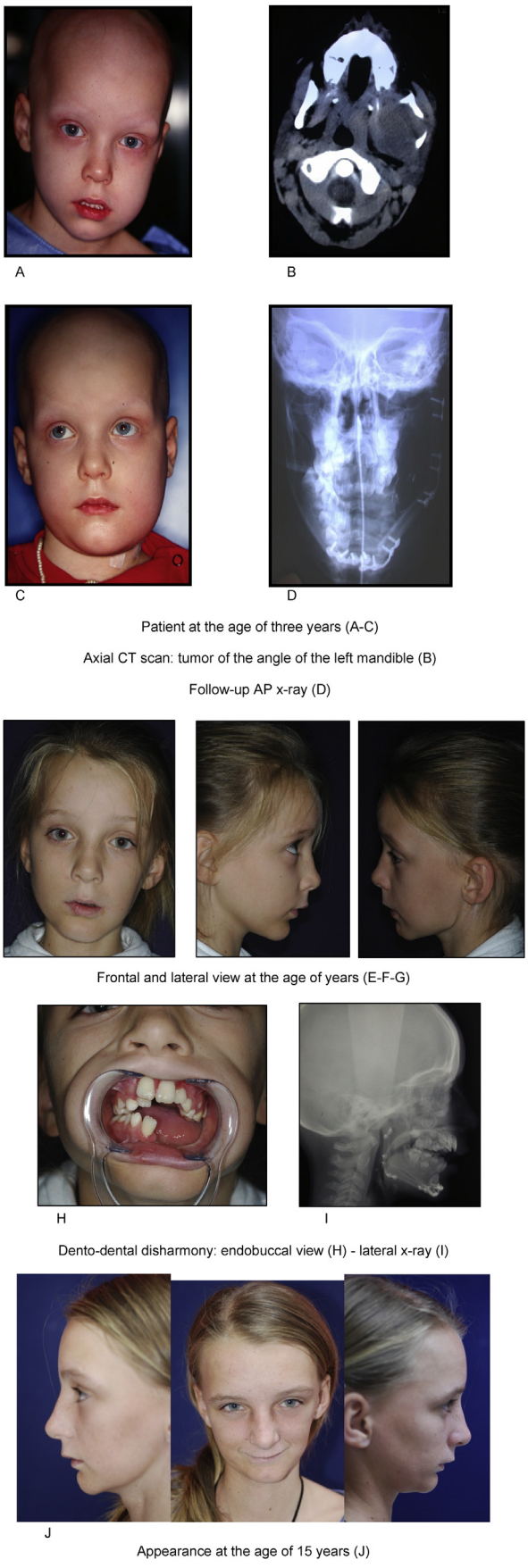


Fig. 6. Patient with mandibular sarcoma treated by chemotherapy followed by surgical resection and reconstruction by free fibula flap.

this article also describes the particular characteristics of the neonatal immune system, which may allow a certain degree of tolerance.

An experimental study on the neonatal pig was conducted to verify this hypothesis, but unfortunately concluded that the immunological status of the neonate is not sufficient to allow tolerance of the graft without immunosuppressive therapy and that the risks of rejection and death of the animal increase with increasing age and weight. However, these authors raised some interesting concepts, although not applicable to the face, when they described the hypotrophic nature of the residual stump and the "impossible" cognitive integration of the transplant. In relation to this last point, autologous transplantation has been shown to allow cortical integration of transfer of the second toe to replace a missing thumb or fingers. However, the fact remains that there is no true aplastic malformation of the face, possibly apart from certain severe forms of first pharyngeal arch syndrome. And, a remarkable point, facial allotransplantation can only claim to achieve satisfactory results on a frontal, mirror image view, with less favorable results on a profile view.

5. Conclusion

The question mark included in the title highlights the risk of conjecture in medicine and surgery, a trap which was not avoided by the National Ethics Advisory Committee in 2004 in its opinion 82 when it refused the very term "face graft" and issued a strongly negative opinion to implementation of this technique.

Composite tissue allotransplantation of the face only has any meaning if it consists of face graft, if, by reconstituting the form and function of the destroyed organ, it allows the disfigured subject to reconstruct his or her integrity, regardless of the subject's age.

These questions raised specifically in relation to facial transplantation in children are based on a retrospective review by a surgeon who has managed several cases of extreme disfigurement in children. However, this retrospective view is worthless, even when backed up by experience with adult transplantation. It is only unimagined and unimaginable circumstances, which, as in adults, will impose the need for face transplants in children, raising new questions that are currently unimagined and unimaginable. All other positions would be erroneous.

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