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Does pediatric hand transplantation undermine a child's right to an open future?

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ABSTRACT

To date, pediatric hand transplantations have only been performed twice. The ethical issue most often discussed in the literature on this surgery concerns the risks of immunosuppression. While these risks are significant, they can be at least partially mitigated by selecting for patients who are already immunocompromised. Nevertheless, as we will argue, pediatric hand transplantation raises ethical issues that go beyond the risks of immunosuppression. In this paper, we focus on three additional ethical issues: the fact that pediatric hand transplantation aims to improve, rather than save life; the fact that it is an experimental surgery; and the fact that it will be performed on non-autonomous patients whose 'right to an open future' may potentially be undermined by the surgery. Taken together, we think that these considerations suggest that transplantation should be postponed until a child is mature enough to make their own decision about it.

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Although over 70 patients have received hand or upper extremity transplantations [1], pediatric hand transplantations have only been performed twice. The first monolateral pediatric hand transplantation was performed in 2000 on a newborn girl immediately after birth to correct a congenital deformity. The donor was her deceased identical twin, making immunosuppression unnecessary [2]. The first bilateral hand transplantation was performed in 2015 on an 8-year-old boy who was already on anti-rejection therapy following an earlier kidney transplant [3].

Pediatric hand transplantation raises significant ethical issues, which may partially explain why it has not become a viable clinical option [2]. The ethical issue most often discussed in the literature has to do with the risks of long-term immunosuppressive therapy, which would be required to keep the transplanted limb from rejecting [2]. While these risks may often be significant enough to rule out pediatric hand transplantation as an ethically viable option, they are less ethically decisive in cases like the two that have been performed. In those cases, the risk of immunosuppression therapy was either not present, or was not believed to be heightened by a hand transplantation.

In this paper, we seek to move the ethical discussion surrounding pediatric hand transplantation beyond concerns about the risks of immunosuppression therapy. In doing so, we raise three considerations that we think will be relevant to all cases of pediatric hand transplantation, and not just to cases requiring immunosuppressive therapy. The first two concerns relate to the procedure itself: we should be concerned that pediatric hand transplantation aims at life-improvement, rather than life-saving, and that as such, it requires patients and their parents to make complicated calculations about what it means for their life to be concerned. In addition, we should also be concerned that the experimental nature of the surgery will make it especially difficult

to perform and communicate these calculations. The third concern relates to the limits of parental medical decision-making. Specifically, we question whether parents ought to be allowed to consent to life-improving, experimental surgeries like pediatric hand transplantation, and whether pediatric hand transplantation ultimately respects or violates a child's 'right to an open future'. In discussing these issues, we identify relevant results from the empirical literature, and raise further questions for medical and ethical experts.

Because we are concerned with ethical issues raised specifically by pediatric hand transplantation, we will not consider questions concerning the prioritization of hand transplantation relative to other procedures, or the allocation of resources for clinical practice or research. Our discussion will assume that the cost of pediatric hand transplantations could be covered by private insurance or government, and thus will not represent an undue burden on either the patient or their family, and that it will be possible to ethically procure hands for transplantation.

Life-improving transplantations

Pediatric hand transplantation is a surgery that aims to improve, rather than save, life. While any type of transplantation carries with it various risks, it may be more difficult to weigh these risks against potential benefits in the case of life-improving transplantations than in the case of life-saving transplantations. The risks associated with receiving a life-saving transplantation are almost always outweighed by the risks associated with *not* receiving it. In contrast, as Caplan and Purves note, life-improving transplants require a more complicated cost-benefit analysis that involves weighing quality of life against quantity [4], and that requires patients to make judgments about how various experiences with

which they have no direct acquaintance (the experience of having two hands, the experience of rejection, etc.) will impact their quality of life. Patients may also be prone to wishful thinking or cognitive biases [4].

The issues that Caplan and Purves [4] raise with life-improving transplantation are compounded in pediatric cases. This is because the person making the decision will not be the one receiving the transplant. Parents may struggle to make decisions on behalf of their child, because they lack direct experience of being an amputee, and because they may not be able to accurately assess how their child understands 'quality of life'. They may also fall victim to the 'disability paradox': while many people without disabilities routinely associate being disabled with having a poor QoL, people with disabilities often report having a high QoL [5].

These concerns can both be partially ameliorated in two ways. First, extensive psychiatric screening must be performed on potential patients and their family, to select against candidates who have unrealistic expectations and who are likely to struggle with post-operative compliance. This is already standard in adult hand transplantation. Second, assent from the pediatric patient must be sought, when possible. In doing so, we should be concerned that the child may not have sufficiently developed value preferences to make judgments about how to balance competing harms and benefits. We must also work to ensure that the child is not subject to undue parental influence, given that the nondisabled parent may have a different view of disability than the disabled child [5–9].

Both of these solutions will require that patients and their families be presented with informative, and age-appropriate data about the procedure. This is difficult, given that it is an experimental procedure with limited data. It is to this issue that we shall now turn.

Experimental surgery

The surgical techniques involved in pediatric hand transplantation have been used for adult hand transplantation and pediatric replantation, neither of which are considered experimental. Nevertheless, given the lack of data on the risks and benefits of pediatric hand transplantation, it should be classified as an experimental procedure. The fact that 'pediatric' hand transplantation would be an experimental procedure compounds the ethical issues associated with life-improving transplants. Because the procedure is experimental, it will be difficult to provide accurate information about risks and benefits, and thus to temper wishful thinking. Nevertheless, a survey of similar procedures will be useful to determining the risks and benefits of pediatric hand transplantation.

This section will examine data from three similar procedures (pediatric autologous replantation, adult hand transplantation, and pediatric renal transplantation), and will consider how these data may be applied to the case of pediatric hand transplantation.

Pediatric transplantation may initially seem similar to pediatric replantation, which is not considered an experimental procedure. Nevertheless, there are several salient differences between the two procedures. Hand transplantation requires a more multi-disciplinary approach, involving more complex organization, than is involved in replantation. As well, during a transplantation, surgeons must deal with bone mismatch, muscle atrophy, and some degree of tissue fibrosis [10]. These factors are not present in the replantation case, and they serve to make the functional results

of hand transplantation uncertain. The data on adult hand transplantation and replantation suggest that pediatric transplant recipients will require more post-surgical support than replanted patients, including immunosuppression (if not already immunosuppressed), rehabilitation, occupational therapy, and psychological support [11]. Conversely, some of the risks associated with pediatric replantation will not be present in the transplantation case. Replantation is often performed under emergency conditions, whereas transplantation allows for advance planning. Given these differences, we suggest that data on adult hand transplantation can give us a more accurate, but still very incomplete, picture of the risks and benefits of pediatric hand transplantation.

The primary risk associated with hand transplantation is not surgical, but rather results from immunosuppression [4]. Immunosuppressive therapy can increase the risk of cancer, infection, metabolic disorders, kidney disease, osteoporosis, cardiovascular disease, and growth retardation, thus shortening life [12–14]. One might think that this risk can be fully mitigated by selecting transplant candidates who have previously received a transplanted organ, and are thus already immunosuppressed. This is incorrect, as even immunosuppressed patients may require additional therapy if their transplanted limb begins to reject. This happened to the 8-year old boy who received a bilateral hand transplant in 2015. Prior to transplantation, the child was receiving a steroid-free anti-rejection protocol [2]. After the second allograft, he had to be placed on an immunosuppressive therapy protocol that included steroids, which increased his risk for bone necrosis and growth retardation [2].

There are additional risks associated with selecting candidates who have previously received organ transplants. For instance, human leukocyte antigen mismatching is considered a significant contributing factor to sensitization, which can lead to reduced retransplant rates and increased time to retransplantation [15,16]. Pediatric hand transplants may increase the risk of HLA-mismatching in previously transplanted patients, thus also increasing the risk of sensitization. This means that pediatric hand transplantation, which is meant to improve life, may end up being a major limiting factor to kidney retransplantation, which aims to save life. How clearly this can be explained to a young child may represent a further challenge for proper patient assent.

In addition to being concerned about the effect that a transplanted hand may have on previously transplanted organs, we should also consider the survival of the hand itself. In the adult hand transplant case, the long-term graft survival rate is relatively high. Shores et al. [1] report that, in the United States and Western Europe, the long-term graft survival rate is 83.1%. Out of 107 limb transplants performed on 72 different patients between 1999 and 2015, 22.4% have suffered graft loss because of patient's death, acute limb loss, or chronic limb loss [1]. These rates are slightly higher than the rejection rates reported in pediatric renal transplants (the 5- and 10-year graft survival rates have been reported as 78% and 60% respectively) [16].

When the limb is ultimately rejected, the patient will once again be an amputee. The patient's history of amputation, along with the damage sustained to the graft site during the original surgery, may make them a bad candidate for future transplants [5]. Indeed, to date, there have been no retransplantations performed on adult patients. That a previous transplantation may make someone a bad candidate for future transplantations is a risk present in all hand transplant cases. Nevertheless, it is especially worrying in the pediatric case for two reasons. First, pediatric transplant recipients may require retransplantation more frequently due to improper growth and limited graft durability

[5]. There is currently no way to know whether bone growth in the transplanted hand will be normal, although evidence from pediatric kidney transplants suggests that approximately one half of transplanted children have shorter than average stature, likely due in part to corticosteroid therapy [17,18].

Second, pediatric patients often struggle with immunosuppressive therapy compliance. Non-adherence to medication is a significant issue in pediatric transplantation [19–21], and has been associated with approximately 44% of all graft loss and 23% of late acute rejection episodes experienced by pediatric kidney recipients [19].

As the adult transplant case demonstrates, pediatric hand transplantation will likely also offer benefits, such as increased functionality, enhanced social relationships, and enhanced sensory experiences [22]. Unilateral amputees could also potentially experience a reduction in contralateral limb overuse injuries [23,24]. Further, the limited data that have been collected on adult hand transplant recipients paints an optimistic picture of life after transplantation. Those centers [25–28] that have had the largest experience in adult hand transplantation, with case-series of five or more patients, report improvements in quality of life, motor and sensory function. For instance, quality of life was assessed by French [25,28] and Polish [26] groups using SF-36 (Short Form 36) and SWLS (Satisfaction With Life Scale), respectively, and both resulted in scores comparable to the healthy general population. The Polish team [26] assessed the patients both pre- and post-operatively, finding better results after surgery. The French team [25,28] also evaluated activities of daily living and found improvements in patients who underwent bilateral hand transplantation.

Several teams [25–27] reporting on hand motor function after either unilateral or bilateral hand transplantation have observed the achievement of useful motor hand function with variable follow-up periods. Unfortunately, the low number of patients makes it difficult to draw conclusions with clear statistical support. There has also been no data collected concerning the loss of functionality that adult transplant recipients may experience once the graft rejects. This lack of data is concerning for the pediatric case, as graft rejection may occur by the time these patients are young adults.

Because pediatric transplantation is an experimental surgery, our discussion of the risks and benefits associated with it leave us with many unanswered questions, such as: What will the average lifetime of a hand transplant be? Will hands that are transplanted with the growth plate continue to grow along with the rest of the body? What are the additional risks posed by the new induction of immunosuppression that is required for every new transplantation? Are there ways to mitigate the risk that patient non-adherence presents to transplant survival, and how can this risk be presented in the consent and assent process? Will a previously transplanted child, after their transplant ultimately rejects, have the same ability to function as an adult amputee that they would have had if they had never received the transplant? And will they be a candidate for additional transplantations? Questions about long-term risks associated with experimental forms of transplantation will always be difficult to answer, but they are especially pertinent when a transplantation aims at improving, rather than saving life.

Pediatric patients, autonomy, and the right to an open future

Even if these questions could be satisfactorily answered, it is still unclear whether parents should be allowed to permit their

children to undergo this procedure. While parents regularly make medical decisions for their children, there are limits placed on the decisions which they can permissibly make. For instance, while parents may consent to have their young child receive a life-saving transplant or a cochlear implant, a parent may not consent to purely elective cosmetic surgery for their child.

One way to distinguish the types of life-improving surgeries that parents may permissibly allow their children to undergo from the types that they may not is to consider the extent to which different surgeries increase or decrease the range of opportunities that will be available to the child in the future. When parents must paternalistically make decisions for their children, they ought to do so in a way that will likely increase, or at least not unjustifiably restrict, the range of options available to their child later in life: in doing so, they respect the child's 'right to an open future' [29–31], i.e. their right to someday be able to autonomously select amongst a suitably large range of plausible choices about how to live.

It has been argued that parents can reasonably choose to give their deaf children cochlear implants on the grounds that these implants preserve, rather than undermine, their children's right to an open future [31,32]. And because the effectiveness of cochlear implants decreases with age [33], it could be argued that parents who opt for a cochlear implant are not taking away a choice that their child would otherwise have available to them if they choose not to act: if they wait until their child is able to make the decision for themselves, the implant will be much less effective.

Pediatric hand transplantation might be thought to be similar to the cochlear implant case, insofar as it may expand the range of options available to a child [34–36]. Nevertheless, as we have suggested previously, the evidence on this point is mixed. Pediatric hand transplantation may actually have the potential to *decrease* the range of options available to the child. First, even if there are benefits to early transplantation, there is still a concern that the limited lifespan of the transplanted hand might ultimately *reduce* the range of options available in life to their recipients, contrary to its intent. As noted in the previous section, pediatric hand transplants likely carry a significant risk of rejection. A child who receives a hand transplant at age four may be an amputee again by age 27, at which point they will face a high risk of functional (phantom limb pain) and psychosocial problems (anxiety, depression) that are common in young adults following surgical amputation [37–40]. Further, because they are experiencing amputation as an adult, their future options may actually be more constricted than they would have been had they not received the transplant as a child. They may have to suddenly change career paths, and will have to undergo extensive occupational therapy, and learn how to navigate their social life as a new amputee. These are experiences that they would not have had to undergo had they not been transplanted as children. A decision meant to promote the future autonomy and wellbeing of the child, in other words, may end up doing exactly the opposite.

Second, the very act of permitting a transplant on the child's behalf takes away an important decision from a child that would otherwise be theirs to make at a later stage of life. If they wait, the parents can let their child decide whether the benefits of hand transplantation are worth the costs of immunosuppression, hospitalization, and eventual rejection. Alobi et al. [41] have found that many adult amputees, once informed of the risks of hand transplantation, opt not to undergo it. Data on prosthesis use in children, further, suggest that there may be a gap between a parent and child's preferences concerning the child's limb. While

parents report high degrees of satisfaction with their children's prostheses [6], children nevertheless regularly abandon their prosthesis or choose only to use it for specific tasks [6–9].

The prostheses case raises questions about whether or not a parent's preference for hand transplantation will mirror the preference that the child will ultimately have. Further, unlike with cochlear implants, we do not have data on whether the age of transplantation affects the level of functionality achieved following hand transplantation. These data will be ethically difficult to obtain for reasons discussed in the previous section.

These considerations are not ethically definitive. Immunosuppressive therapy could improve within the next ten years, thus reducing the chances of rejection. As well, there may be functional benefits to be gained from early transplantation [3]. Nevertheless, while the extent to which pediatric hand transplants promote or undermine a child's right to an open future may be difficult to predict at the time of transplantation, the fact that pediatric transplantation has the potential to significantly infringe upon this right should make us hesitant about performing it. From this perspective, pediatric life-improving transplantations should generally be postponed until the patient is mature enough to request it themselves.

Conclusions

Pediatric hand transplantation raises significant ethical challenges. When assessing candidates for this form of transplantation, we should be concerned about wishful thinking of behalf of the prospective patient, or the patient's medical decision-makers, about the difficulties involved in providing an accurate picture of the risks and benefits given the experimental nature of the surgery, and about the possibility that the surgery might restrict rather than expand the range of life options available to the recipient over time. In all cases, appropriate information should be provided (although this may not be possible in experimental cases), and psychological evaluation should be performed in order to exclude the possibility of a wishful thinking of the prospective patient and their family. If possible, transplantation should be postponed until the child is mature enough to make a decision about it for themselves.

Disclosure statement

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