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REVIEW

First Human Head Transplantation: Surgically Challenging, Ethically Controversial and Historically Tempting – an Experimental Endeavor or a Scientific Landmark?

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ABSTRACT

According to many, head transplantation is considered to be an extraordinary and impossible surgical procedure. However, nowadays, relevant literature and recent advances suggest that the first human head transplantation might be feasible. This innovative surgery promises a life-saving procedure to individuals who suffer from a terminal disease, but whose head and brain are healthy. Recently, the first cephalosomatic anastomosis in a human model was successfully performed, confirming the surgical feasibility of the procedure, but still not the real outcome. Skepticism and several considerations, including surgical, ethical and psychosocial issues, have emerged in the scientific community since this imaginary procedure seems to be more feasible than ever before.

Keywords: first, head, transplantation, human.

INTRODUCTION

In the past, head transplantation used to be a product of imagination described in science fiction scripts. Nevertheless, nowadays, things have changed and a new era seems to have risen. Human cephalosomatic anastomosis and transplantation has never been realized before due to the inability of fusion regarding the spinal cords of the donor and the recipient. Innovatively, according to the allegations of Canavero *et al*, recent advances (ultrasharp neurosurgical blades, application of fusogens, electrostimulation) can

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confront this obstacle and make such a challenging procedure to be feasible and worth attempting (1).

The goal of the first human head transplantation is to provide a life-saving procedure to patients who are terminally ill without any indication of pathology concerning the head or the brain, on the background that there is no other treatment (2). As a result, several considerations including major surgical, ethical, psychosocial and immunological dilemmas have emerged (3).

By critically analyzing the existing relevant literature and expressing our opinion, we hope that this paper will provide a comprehensive overview of the attempt regarding the first human head transplantation and initiate academic discussion and debate, acting thus as a fertilizer through which this new frontier can be observed and approached.

What is the historical background of head transplantation?

In 1908, Charles Guthrie tried to transplant the head of a donor dog onto the neck of a recipient dog without success (4). In 1950, Vladimir Demikhov developed several surgical techniques concerning transplantation for vital organs and limbs in dogs (5). In the 1970s, Robert White performed the first cephalic exchange transplantation in the monkey by transplanting the head of a rhesus monkey on the body of another headless one. The monkey survived for 8 days with restoration of basic sensations such as smell, taste, hearing, and motor function in the face of the transplanted head (6, 2). Recently, Hirabayashi *et al*, Sygawara *et al*, and Niu *et al* made head transplantation in rats in order to evaluate the brain function after ischemia (7-9). Additionally, Ren *et al* described a surgical approach for head transplantation in a mouse model (10). Finally, Canavero S *et al* described a model for head transplantation in human beings (11, 1). In 2017, Ren *et al* performed successfully a cephalosomatic anastomosis using a human cadaver (12). The papers mentioned above constitute reports, experiments, surgical techniques or even patents setting the historical, theoretical and practical background in the attempt to approach the first human head transplantation.

Who should be qualified for head transplantation?

We agree that the first attempt should be performed in a young person suffering from a terminal disease which leaves the brain and its functions intact such as progressive muscular dystrophies. The donor would be a young brain-dead patient with healthy organs of the same height, matched for immunotype and screened for any systemic disorder. The aim is to perform a removal of the head from the recipient and detachment of the body from the donor, respectively, and accomplish transplantation of the recipient's head onto the healthy donor body (1, 2).

Which are the surgical steps of the procedure?

The following steps present a possible scenario of the procedure according to the surgical protocol suggested by Canavero *et al* (1, 12).

Two surgical teams participate and work simultaneously in order to conduct the procedure. Recipient and donor are intubated, tracheotomized, ventilated and stabilized into rigid fixation. ECG, EEG, monitoring of oxygen saturation, body temperature and hemodynamic monitoring are set. Burst suppression pattern is achieved in the recipient with the use of barbiturate or propofol. Recipient's head is subjected to profound hypothermia (10°C), while donor's body only receives spinal hypothermia avoiding ischemic damage to the rest of the body. In order to achieve profound hypothermia, the technique of autocerebral hypothermic perfusion with the application of a heat exchanger in a femoral-carotid arterial shunt has been described. Also, the biventricular cooling system for deep brain hypothermia has been proposed. Additional help is provided with the use of cooling helmets. Donor's spinal cord hypothermia can be achieved via perfusion of subdural and epidural spaces with cold solutions. Profound hypothermia lowers significantly the metabolic rate of organs and tissues and gives time to surgeons to make the cephalosomatic anastomosis.

Each patient's neck is carefully prepared by the two surgical teams. Three surgical phases can be recognized; the anterior and the posterior approach both in the recipient and the donor, and

the chimera anastomosis. Beginning with the anterior approach, the carotid, vertebral arteries and jugular veins are exposed and all muscles in both recipient and donor are prepared and marked for later linkage. The trachea and esophagus are recognized and surgically prepared through different cervical incisions. The recurrent laryngeal nerves are recognized and preserved intact. In the posterior approach both the recipient and the donor are placed in a prone position. Then laminectomies are performed, the vertebral bodies or the intervertebral spaces are transected, and the dura is cut exposing the spinal cord. Afterwards, under microscopic guidance, the spinal cords in both patients are transected with an ultrasharp microsurgical blade.

The recipient's head is separated, exsanguinated and flushed with iced Ringer's lactate (in order to avoid coagulation complications), then transferred onto the donor's head-less body attached with tubes that connect it to the donor's circulation, within the hour. The anterior spinal stabilization is performed with an anterior plate. Immediately after that, the two spinal cords are fused with a chitosan-PEG (polyethylene glycol) glue which has the ability to immediately reconstitute cell membranes damaged by mechanical injury. Simultaneously, PEG is infused into the donor's blood circulation in order to offer significant amount of polyethylene glycol into the intravascular space as well and promote better neuronal fusion. Sutures around the joined cord are applied. A second iv injection of PEG is administered after 4-6 hours.

The vascular anastomosis between the recipient and donor is conducted through carotid and jugular silastic cannulae. The vascular tubes are removed and sutures are applied on the vessels of the transplanted head together with those of the new body. The donor's circulation provides blood to the recipient's head.

The dura is sewn and a spinal cord stimulator is secured to the dura. The posterior stabilization is performed with a lateral mass screw-and-rod system. Trachea, esophagus, vagus and phrenic nerves are reconnected. Finally, all muscles are linked and the skin is sewn.

Recipient is then brought to the intensive care unit with a cervicothoracic orthosis brace.

Which obstacles are we facing?

Surgical Considerations

Donor body selection

The system for finding the donor body has not been created for such a procedure. However, face transplantations can be performed and donor tissues for such a unique part of the human body can be found. Thus, we believe that this obstacle will be surpassed even for head transplantation if the scientific community acquires confidence over the feasibility of the procedure (2).

Head and body interventions on the recipient and donor

These include challenging surgical skills and demanding cooperation-coordination skills which depend on the multidisciplinary team of surgeons (neurosurgeons and neck, vascular, cardiothoracic, orthopedic, plastic surgeons) and the excellent preparation of the surgical protocol (2, 12). Sparing of phrenic nerves, recurrent laryngeal nerves, vagi, and cervical plexus is demanding and time-consuming, but very important postoperatively mainly for spontaneous respiration and phonation. Various vascular anastomoses, esophagus anastomosis, spinal cord reattachment and spinal cord fixation are demanding surgical steps which elevate the operation's level of difficulty. Bleeding, infections, anastomotic leaks are common post-operative complications. Another crucial point that raises concern and needs to be studied and discussed is the exact cervical myelomere where the spinal cord is going to be transected.

Ischemia time

Maintaining the blood flow to the recipient head and donor body can be achieved using various ways, on the background of hypothermia, up to the point of the reattachment of the vessels between the recipient and the donor. Extracorporeal circulation machine could be the first choice. However, several techniques such as the autocerebral hypothermic perfusion have been proposed in order to achieve profound hypothermia. Continuous cross-circulation between the recipient and the donor is being tested. Additionally, the level of hypothermia and the ideal temperature is still under discussion. It is true that one of the key elements for head

transplantation is to decrease the temperature of the recipient's head to a sufficiently low level that enables disconnecting and reconnecting it to the donor's body under proper conditions, something which has been taken into serious consideration in the proposed protocol (1). The other crucial factor is time. Nevertheless, the protocol is based on previous similar experiments and it is well designed, appearing promising enough to be implemented and be successful (1, 12). Interestingly, Li *et al* evaluated the long-term immune rejection and avoidance of ischemic events during the head transference phases and for those objectives they developed a bicephalic model of head transplantation (13).

Spinal fusion and spinal cord reattachment

A crucial point of discussion is the need for proper mechanical alignment of the severed axons. The surgeons would cut the spinal cords with an ultra sharp blade promising a "clean cut", which will have a crucial role in the fusion of severed axons and in the spinal fusion in total. One way to enhance neuronal recovery is by installing an epidural spinal cord stimulating apparatus (1, 14). Additionally, a pivotal role is attributed to the interneurons which are thought to promote functional recovery through the creation of interconnections between axons. Precision in the reattachment (alignment and proper distance of the reconnected spinal cords) could be perhaps the most important step for the outcome of the procedure.

Post-operative issues

After surgery, the patient will be monitored in the intensive care unit under ventilatory and circulatory support. The stability of the head and the spinal column is a major concern in order to reassure the successful spinal cord fusion. When possible, intensive rehabilitation for quadriplegia should be started. Another major issue is the presence of neurogenic shock due to the alteration in the function of the sympathetic nerves and of the vagus. Paralytic ileus and neurogenic bladder are possible postoperative complications. Long-term ventilatory support may be necessary due to the fact that function of the diaphragmatic muscle may be problematic for an uncertain period of time. After the initial phase, a spinal cord injury rehabilitation protocol should be performed, ideally in the specialized environment of spinal cord trauma unit (2). The possible presence of tracheotomy may cause problems in the rehabilitation and in the quality of life. Vocal cord function may present problems affecting communication and self esteem. Additionally, the onset of cord central pain is a possible postoperative complication because of the transection of the spinothalamic tract (1, 15).

Ethical considerations and public aspect

Scientific and public criticism

It is known that the initial scientific and public reaction to the first kidney and heart transplant was as "playing God" and violating the rules of nature. Nowadays, we face a similar reaction (14). It is true that, in the history of medicine, many examples of ideas were initially rejected and later were adopted, thanks to the persistence of their researchers despite criticism (16, 2). Indeed, several studies have expressed their doubt, about the feasibility and correctness of the procedure (17-19). Specifically, the EANS Ethico-legal Committee finds the proposed head transplant project unethical (20). After open and unbiased dialogue within the scientific community, mutually accepted ethical criteria could be proposed for this project avoiding unnecessary criticism.

Immunosuppresion and ethics

Theoretically, head transplantation, when performed in patients with terminal conditions but intact brain function, would be life saving. Possible risks associated with the immunosuppression could be justified if we consider that, theoreticaly, head transplantation could be a life saving procedure. We could take into consideration that immunosuppresion induced risks are ethically acceptable for vital organ transplantations after years and series of research studies and evidenced-based medicine (14). Additionally, operations such as hand and face transplantation have curved the route for approaching the ethical aspect of head transplantation by pushing to the limit the ethical boundaries which necessitate or justify a procedure like this.

Moreover, it is important to mention that the dose of immunosuppressive substances may be extremely high causing multiple effects on the

recipient. To be more specific, in case of calcineurin inhibitors, there is a great possibility that they may cause nephrotoxicity or even end-stage renal disease due to high dosage. Another consideration is the possibility of somatic rejection and, in that case, the level of immunosuppression dosage with the associated increased risks.

Lack of experimental data

The scientific debate on this topic remains silent, maybe because there is a lack of research in the relevant literature. Only a few independent papers have been published. The majority of them are opinions or surgical techniques under testing. Experimental data are almost absent. These facts have a negative consequence in the feasibility of the procedure.

Without convincing scientific data, the scientific community cannot proceed to the deployment of approved protocols. Thus, the possible consent by the patient will not be based on jointly approved medical criteria and indications; however, the consent will rest in the ignorance and desperation of patients who are unable to recognize, or overlook, the risks of head transplantation (3). The scientific community should accept the presence of debate regarding the feasibility of the project and encourage studies that will produce experimental data in order to approach and evaluate the procedure.

Cost

Someone may say that head transplantation could be considered an operation with vast costs and ambiguous efficiency. Cost is regarding medical and nursing stuff as well as materials for the operation. With respect to head transplantation, the body used in this operation could provide multiple vital organs such as lung, liver, heart, kidney, hands, face and tissue to save many lives. It is known that we are facing a shortage of organs which could save the life of many patients worldwide. With a proper donor procurement system, this problem could be balanced. This system should be regulated by using ethical, medical criteria and protocols in order to provide the maximum of vital organs to those in need and prevent deaths of patients in the waiting list for organ transplantation.

Psycosocial considerations

Social service

In case of successful outcome, patients will require long-term extensive rehabilitation and physical therapy due to muscular atrophies. The recovery in terms of sensory and fine motor function is crucial for the post-operative amelioration of the patient's condition. Social services have to offer assistance by providing a long period of unemployment, healthcare insurance, aid in the income, assistance to the family. There are many possibilities that, following a successful head transplantation, the patient will still face a quality of life and well-being problems with continuity of quadriplegia for an uncertain duration (2).

Psychological aid

After transplant, confusion may be created about the relationship between body and identity in the recipient, suggesting the need for mental health assistance by psychiatrists (21, 2). Additionally, self-esteem problems because of cosmetic reasons (scars, asymmetries) might evoke. Given the high probability of death intra- or post-operatively, the family will require psychological preparation for the possibility that the patient will not survive surgery.

Secondary issues

Head transplantation may have legal obstacles as well. In the future, the offspring of a patient who has been subjected to successful head transplantation may pose questions regarding inheritance and parental custody (2). Reproductive implications of human head transplantation have also emerged (22). In addition, some have pointed out religious barriers (23). Another consideration is whether it should be ethical to perform head transplantation between patients of different genders. In that case, identity issues are even more complicated for the recipient.

What should we expect?

Ren and Canavero have answered to various queries and have expressed their certitude for the feasibility of the procedure (24). Recently, Ren *et al* reported that the first cephalosomatic anastomosis has been successfully performed in

a human cadaver, confirming the surgical feasibility of the procedure and further validating the surgical plan (12). The surgical protocol took 18 hours to complete and acted as a full rehearsal, helping in the optimization of surgical steps. Additionally, Liu *et al* have concluded that a sharply and fully transected spinal cord can be successfully reconstructed, having as a result partial recovery of motor function and electrical continuity in large animals (25). Sergio Canavero had claimed that he would have conducted the procedure by 2017; moreover, this has not been performed on a living human until now.

Although these papers present promising results, factors such as testing of the surgical protocol in a cadaver, level of reconstruction of the transected spinal cord and variability between the species are major hurdles, which make questionable the assumption of feasibility in a living human. There are key elements in the procedure, such as functional spinal cord fusion, sufficient neuroprotection and post-operative pain control, which are still in doubt (26). Nevertheless, we should admit that the consideration of a "clean cut" with an ultrasharp blade and application of fusogens are significant pieces in the puzzle, but they need to be further studied. The literature still provides not enough data and more experimental studies in human cadavers and animals should be conducted.

Sooner or later, the procedure is imminent. However, under the current circumstances, the first attempt would be unethical if it occurred. For this reason, the discussion over the preparation of proper ethical codes for this specific operation is extremely important. As Farhud D. has stated, the medical world should be ready to face primarily the psychosocial (identity-personality-behaviour issues, mood disorder, psychosis, suicide) and ethical (autonomy, beneficence, non-maleficence, justice) challenges (27).

The scientific community should not consider this procedure as a product of imagination anymore, but as a current topic that raises concerns and needs to be analyzed. Reputed and specialized surgeons from different countries and fields of surgery should express their opinion and enlighten any corner of ambiguity. Each step of the procedure should be extensively studied. A scientific discussion should be initiated in order to engulf the project, evaluate it, balance ethical dilemmas and engage in experimental studies on cadavers and animals. The first attempt must not be done hurriedly, but it should be performed as a well designed, tested and scientifically mature protocol with significant possibilities for success. Maybe the next step would be a procedure on a heart-beating brain-dead donor in order to rehearse the operation in a live patient.

Apart from the feasibility of the procedure and the ethical obstacles, there is one more thing we should consider: the unnecessary controversy and acrimony towards the procedure. Probably, the existing skepticism is a product of our own insecurities with respect to something new and challenging. We should think whether we are ready or not to surpass not only the practical obstacles but also our doubts and fears. By giving a chance to this procedure, maybe we accept the failure of recent advances and medicine in general, as Ren and Canavero have stated: "When you have to change a body because you cannot fix it, that is a sign of failure." (16).

Are we ready to accept the recent advances and make a step forward? Are we ready to handle our incompetence to confront with terminal diseases and give a solution? ❑

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