International Journal of Surgery 41 (2017) 196–202

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Review

The immunologic considerations in human head transplantation

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HIGHLIGHTS

- Head transplantation appears at first as unrealistic, unethical, and futile.
- Surgical, ethical, psychosocial, and immunologic hurdles associated with head transplantation are enormous.
- Immunologic considerations associated with head transplantation are discussed.
- This review will give readers insight into immunologic opportunities and challenges facing head transplantation.

ARTICLE INFO

Article history:
Received 23 November 2016
Received in revised form
19 January 2017
Accepted 20 January 2017
Available online 24 January 2017

Keywords:
Head transplantation
Composite tissue allotransplantation
Vascularized composite allografts rejection
Tolerance
Reconstructive transplant surgery
Frontiers in surgery

ABSTRACT

The idea of head transplantation appears at first as unrealistic, unethical, and futile. Here we discuss immunological considerations in human head transplantation. In a separate accompanying article we discuss surgical, ethical, and psychosocial issues concerned in body-to-head transplantation (BHT) [1]. The success of such an unusual allograft, where the donor and the recipient can reject each other, depends on prevention of complex immunologic reactions, especially rejection of the head by the body (graft-vs-host) or probably less likely, the possibility of the head rejecting the total body allograft (host-vs-graft). The technical and immunologic difficulties are enormous, especially since rapid nerve and cord connections and regeneration have not yet been possible to achieve.

In this article we begin by briefly reviewing neuro-immunologic issues that may favor BHT such as the blood brain barrier (BBB) and point out its shortcomings. And we touch on the cellular and humoral elements in the brain proper that differ in some respects from those in other organs and in the periphery. Based on recent successes in vascular composite allografts (VCAs), we will elaborate on potential specific advantages and difficulties in BHT of various available immunosuppressive medications already utilized in VCAs. The risk/benefit ratio of these drugs will be emphasized in relation to direct brain toxicity such as seizure disorders, interference, or promotion of nerve regeneration, and potentiation of cerebral viral infections. The final portion of this article will focus on pre-transplant immunologic manipulation of the deceased donor body along with pretreatment of the recipient.

1. Introduction

The idea of head transplantation appears at first as unrealistic, unethical, and futile. Here we discuss immunological considerations in human head transplantation. In a separate accompanying article we discuss surgical, ethical, and psychosocial issues concerned in body-to-head transplantation (BHT) [1]. The success of such an unusual allograft, where the donor and the recipient can reject each other, depends on prevention of complex immunologic

DOI of original article: http://dx.doi.org/10.1016/j.ijsu.2017.01.077.
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http://dx.doi.org/10.1016/j.ijsu.2017.01.084
1743-9191/

reactions, especially rejection of the head by the body (graft-vs-host) or probably less likely, the possibility of the head rejecting the total body allograft (host-vs-graft). The technical and immunologic difficulties are enormous, especially since rapid nerve and cord connections and regeneration have not yet been possible to achieve.

In this article we begin by briefly reviewing neuro-immunologic issues that may favor BHT such as the blood brain barrier (BBB) and point out its shortcomings. And we touch on the cellular and humoral elements in the brain proper that differ in some respects from those in other organs and in the periphery. The importance of these cellular elements in initiation of allograft rejection and their possible role in allograft acceptance will be emphasized on the basis of data of cellular brain activity found in studies of autoimmune and degenerative brain diseases. Understanding some of these elements in neuro-immunobiology, a growing clinical and scientific field, will have major implications for planning, development, and execution of both experimental and eventually, clinical BHT.

Based on recent successes in vascular composite allografts (VCAs), we will elaborate on potential specific advantages and difficulties in BHT of various available immunosuppressive medications already utilized in VCAs. The risk/benefit ratio of these drugs will be emphasized in relation to direct brain toxicity such as seizure disorders, interference, or promotion of nerve regeneration, and potentiation of cerebral viral infections. The role of the BBB in the action of the various agents will be briefly addressed, particularly in relation to drug interactions, and their access [2] and influence on the effector cells in the brain. We will also briefly comment on the common side effects of the various agents that may have significant systemic adverse effects on the host, such as nephrotoxicity of calcineurin inhibitors. Throughout the text, it is emphasized that the failure of preventing rejection of the head or the body will undoubtedly be fatal and no rescue with a new body will be possible. It is not emphasized, but understood, that the failure of any major organ such as the brain, the heart, the lung, or the liver may also result in a fatal outcome. The final portion of this article will focus on pre-transplant immunologic manipulation of the deceased donor body along with pretreatment of the recipient. The immunologic manipulation of the donor described briefly in this article could eventually be the conceptual strength of this intervention but would first need to be rigorously tested in a large animal model, such as the pig. The pre-transplant immunosuppression of the recipient would aim to alter the donor body's antigen presentation and immunologic mechanisms of rejection of the head and brain to avoid response to the transplanted body, which may also be highly modified prior to transplantation.

2. Brain immunology axis – basis for head/brain transplantation

To address the issue of BHT, we need to understand the “Brain-Immunology Axis” elegantly reviewed by Maria Szalawitz [2]. In her review she looks at the brain as the “body's command center” and at immune responses as being everywhere. In BHT the command center will oversee an unfamiliar body communicating via the vasculature, which is blocked by the absence of neural connections, which carry impulses both from and to the brain. Cells that mediate immune reactions will not cross an uninjured blood brain barrier (BBB) but may communicate with the brain via cytokines present in the vessels. The critical idea that the brain and the immune system are constantly interacting is the major reason to briefly review these various concepts, which illustrate many immunologic unknowns.

The microglial cells, the main innate immune cells in the brain, are the “defenders” of the brain against pathogens and injury; at the same time they produce many pro-inflammatory cytokines. Targeting these cells may be helpful, but also may be dangerous. They are similar to macrophages and express Toll-like receptors (TLRs), and respond to TLR ligands that could be used to inhibit them [3,4]. Suppression of specific TLRs, as with Sirolimus, could control immune injury and could affect the permeability of the BBB to Sirolimus and to calcineurin inhibitors (CNIs) [5]. The interaction of the various cytokines and TLRs are reviewed by Rivest [6]. Immune responses by microglial cells may result in the release of many molecules, even glucorticoids, implicated in graft rejection and acceptance at other sites.

The BBB, thought to account for the brain's “immune privilege” status, once injured, as in ischemia, becomes permeable. It may prevent entrance not only of activated cells, but also of many antibodies. The tight junctions of the endothelial cells forming the BBB could be helpful by denying access to the brain of rejection-causing elements, as long as the BBB is not injured by ischemia. Areas of the brain that participate in hormonal control lack the BBB [7,8] and allow diffusion of large molecules, such as antibodies and immunosuppressive monoclonal reagents, but not cells. The BBB permits passage of Glucocorticoids and Sirolimus (lipid soluble) [5], which may prove to be important in preventing brain injury, nerve healing, and rejection [9–13]. Bone-marrow derived microglial cell precursors (donor) may enter the brain at the site of ischemic injury of the BBB or through CSF, and they can then initiate rejection damage of the brain if they are not altered by pre-transplant manipulation (vide infra).

In vascular composite allografts (VCAs) immunologic manipulation before transplantation (induction), during transplantation (acute), and after transplantation (maintenance), is primarily based on clinical practice [14–18]. The classical concept of acute cellular rejection (ACR) focuses on the role of antigen presenting cells (APCs) and subsequent activated T-cell responses. Analysis of T-cell activity in the brain is best described in relation to the development of autoimmune diseases and is well reviewed by Joan Goverman [19]. It focuses on activation, infiltration, antigen specificity, pathogenicity, and regulation of different T-cell subsets. These may have an important bearing on a brain transplant. Since the brain is protected by the BBB, the body's T-cells will have to be first activated in the periphery by the recipient (head) antigens of the face. Activated and memory T-cells may then be able to move between the tight junctions of the endothelial cells of the BBB and the epithelial cells of the blood -CSF barrier, but they can do so only in the presence of inflammation. The mechanisms of $CD8^{+}$ and CD4+T-cell inflammation and infiltration that may ensue after undesirable effector cells enter the brain have been reviewed previously [19–22]. We propose that much of this may be avoided by manipulating the bone marrow cell precursors of the donor's body to assume the antigenic characteristics of the recipient (head) while the peripheral donor cells are maximally eliminated. Pre-transplant manipulation of the donor into a full, or even a partial, HLA recipient chimera might require immunosuppression only to combat possible graft-vs-host disease.

3. Lessons from vascular composite allografts- the use of immunosuppressive drugs

Prevention of rejection of the head by the body may be paralleled by the head rejecting the body. If we are to learn from VCA lessons [14–18], it has been found that donor T-cells residing in the facial allograft have been the major constituents of rejection [18] and that lymphocyte- mediated injuries to microvessels and various stem-cell compartments predominate [23–25].

Although clinically the head is the recipient in BHT, the deceased