Title
Preliminary report: indications of improved visual function following retinal sheet transplantation to retinitis pigmentosa patients.

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Authors
Radtke, ND
Aramant, RB
Seiler, MJ
et al.

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layer beneath the retinal pigment epithelial cells was the basal laminar deposit, which was characterized by scattered long-spacing banded collagen material, and positive areas around retinal pigment epithelial cells corresponded to basement membrane–like structures (Figure 2). These results show that matrix metalloproteinase-7 may be present in Bruch membrane in choroidal neovascular membranes and strongly implicate matrix metalloproteinase-7 in degradation of basement membranes and neovascularization in the choroid. Matrix metalloproteinase-7 may degrade the extracellular matrix in Bruch membrane and be associated with the perforation of new vessels into Bruch membrane. These results suggest that matrix metalloproteinase-7 and matrix metalloproteinase-2,9 are potentially important factors in the development of choroidal neovascular membranes.

REFERENCES


Preliminary Report: Indications of Improved Visual Function After Retinal Sheet Transplantation in Retinitis Pigmentosa Patients

Norman D. Radtke, MD, FACS, Robert B. Aramant, PhD, Magdalene Seiler, PhD, and Heywood M. Petry, PhD

PURPOSE: To report indications of new visual function after retinal transplantation in two blind patients with retinitis pigmentosa.

METHODS: Intact sheets of fetal retina (15 and 17 weeks gestational age) were transplanted subretinally (between the neurosensory retina and the retinal pigment epithelium) near the fovea in the left eye of a 23-year-old white man (Patient A) and in the left eye of a 72-year-old white woman (Patient B), both with autosomal-recessive retinitis pigmentosa.

RESULTS: Postoperatively, at 6 and 5 months, respectively, both patients reported new visual sensation in the visual field corresponding to the transplant. In both patients, the visual sensation continued to be present after transplantation, at 12 and 8 months, respectively. In Patient A, a transient multifocal electroretinography (mfERG) response was observed in the transplant area 4 months postoperatively but was not detectable in Patient A at 6.0 and 9.5 months post–retinal transplantation. In Patient B, no positive mfERG responses were seen up to 5 months postoperatively. No rejection (presenting as cystoid macular edema, macular pucker, and extensive intraretinal edema with disrupted retinal pigment epithelium) to the transplanted tissue was seen up to 13 months in Patient A and 9 months in Patient B by fluorescein angiography.

CONCLUSION: Transplantation of intact sheets of fetal human retina in two patients with retinitis pigmentosa was not associated with evidence of transplant rejection. Subjective improvement and an indication of objective improvement 4 months postoperatively were seen in Patient A, and subjective improvement only was seen in Patient B. (Am J Ophthalmol 1999;128:384–387. © 1999 by Elsevier Science Inc. All rights reserved.)

RETINITIS PIGMENTOSA IS A GROUP OF HEREDITARY diseases that may result in legal or total blindness. Rod photoreceptors degenerate first, and cone photoreceptors and retinal pigment epithelium degenerate in later stages. Sheets of adult human photoreceptor cells harvested from human cadaveric eyes have been safely transplanted to the subretinal space of two retinitis pigmentosa patients without systemic immunosuppression. However, no improved function has been reported.1

The motivation for this human trial was our success in transplanting intact sheets of fetal retina to restore damaged rat retinas.2 Those transplants developed an organized photoreceptor layer with outer segments in contact with the host retinal pigment epithelium2 and showed a phototransduction protein dark-light shift like normal photoreceptors.3 We have developed a unique instrument and method to

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From the Department of Ophthalmology and Visual Sciences (N.D.R., R.B.A., M.S., H.M.P.), the Department of Anatomical Sciences and Neurobiology (R.B.A., M.S.), and the Department of Psychological and Brain Sciences (H.M.P.), University of Louisville School of Medicine, Louisville, Kentucky. This work was supported by the Vitreoretinal Research Foundation, Louisville, Kentucky (N.D.R.), the Jewish Hospital Foundation, Louisville, Kentucky (R.B.A., M.S.), National Institutes of Health grant RO1EY08519, Bethesda, Maryland (R.B.A., M.S.), the Murray Foundation, Inc, New York, New York (R.B.A., M.S.), Foundation Fighting Blindness, Hunt Valley, Maryland (R.B.A., M.S.), an unrestricted grant from Research to Prevent Blindness, Inc, New York, New York (Department of Ophthalmology, University of Louisville), and an anonymous donor (R.B.A., M.S., N.D.R.).

Norman D. Radtke, MD, Robert B. Aramant, PhD, and Magdalene Seiler, PhD, have a proprietary interest in the instrument and method (patent pending) discussed.

Reprint requests to Norman D. Radtke, MD, FACS, Retina Vitreous Resource Center, 240 Audubon Medical Plaza, Louisville, KY 40217; Fax: (502) 634-1646; e-mail: NRADTKE@prodigy.net.
transplant flat pieces of fetal retina into the subretinal space between neurosensory retina and retinal pigment epithelium. This technique maintains the correct orientation of the retinal sheets, and the minimal trauma associated with the procedure reduces the possibility of rosette formation or rupture of Bruch’s membrane. This approach has significant advantages over other techniques because we use intact sheets instead of injecting dissociated cells, and we use fetal instead of adult tissue. Fetal cells have outstanding properties. They are well tolerated immunologically by a host of the same species when placed into the central nervous system or the eye because they lack antigenic sites. They have a high capacity to proliferate, sprout processes, and produce trophic substances that aid host and transplant cells to establish contacts, and they also have a greater ability to overcome the trauma of transplantation than adult cells.

Appropriate Institutional Review Board approvals were obtained from the hospital and the University of Louisville Human Studies Committee. Patients receiving the transplant gave informed consent after extensive counseling regarding the realistic expectations of the procedure. At the time of the tissue implantation, Patient A was a 23-year-old white man with autosomal-recessive retinitis pigmentosa, with bilateral visual acuity of counting fingers at 3 feet. Patient B was a 72-year-old white woman with autosomal-recessive retinitis pigmentosa, with bilateral visual acuity of hand motions. Eyes of a 15-week (for Patient A) and a 17-week (for Patient B) gestational age fetus were obtained by informed consent. The tissue was kept cold after harvesting until it was transplanted approximately 6 to 7 hours later. After dissection of the fetal retina, a 1.7 × 3.0-mm piece was cut out and implanted subretinally near the foveas of Patient A and Patient B. A standard vitrectomy surgical procedure was performed, and a 3-mm retinotomy was made approximately 4 to 5 mm away from the planned implantation site horizontally and parallel to the horizontal raphae of the nerve fiber layer. A custom-made implantation instrument was used. The tissue was loaded into a flat plastic nozzle (inner lumen at tip 0.3 mm × 2.0 mm) that was curved at a 135-degree angle. The loaded instrument was inserted under the retina through the retinotomy site and the tissue was placed into the target area.

Complete preoperative assessments (ocular examination fluorescein angiography, multifocal electroretinography [mfERG]) were repeated after surgery. Patient A had two preoperative mfERG tests and postoperative mfERG tests at 1.0, 4.0, 6.0, and 9.5 months. Patient B had three preoperative mfERG tests and postoperative mfERG tests at 3 and 5 months.

Postoperative fluorescein angiography showed no indication of rejection, no delayed hypersensitivity, and no clinical evidence of inflammation in the operated eyes in either patient (Figure 1). Fluorescein angiography can show the integrity of the retinal vessels and retinal pigment epithelium and thus show rejection expressed as abnormality or leakage of retinal vessels, as in cystoid macular edema, macular pucker, optic disc edema, or extensive intraretinal edema with disrupted retinal pigment epithelium.

Multifocal electroretinography, a relatively new diagnostic method introduced by Sutter and Tran in 1992, has applications for diagnosis in patients with retinal disorders. To assess potentially corresponding physiological changes in the region of the transplant, photopic mfERGs (mean luminance, 200 cd/m², 75 Hz frame rate) were recorded using a Burian-Allen electrode (Hansen Ophthalmic Development Library, Iowa City, Iowa) and a VERIS Science 3 system (EDI, Inc, San Mateo, California). A 42 × 38-degree field of 103 hexagons was used, with the hexagons flashing on or off according to a
FIGURE 2. Multifocal electroretinography recordings of the left eye of Patient A. (A) Representation of the 103-hexagon array showing (1) the area corresponding to the transplant, (2) the immediate surrounding area, and (3) the remainder of the stimulated retina. (B and C) Average second-order response waveforms from a 1.3 × 3.5-mm area corresponding to the transplant location (1, in panel A); (2) the immediate surrounding area (2, in panel A); and (3) the remainder of the stimulated retina (3, in panel A). Response latency and response amplitude values at the right correspond to the points indicated on the waveforms. Preoperative waveforms were obtained 3 months before surgery. Postoperative recordings were done 4 months postoperatively. A negative component is apparent at a latency of 30 to 35 msec in the response corresponding to the postoperative transplant area. This response was not seen in the preoperative recordings or in the surrounding retina 4 months postoperatively.
useful approach to restoring vision in patients with retinal degeneration. Caution is recommended in interpreting the significance of the transient mfERG response because it may be related to a fluctuation in the disease process and not caused directly by the tissue transplantation. Subsequent work with more patients will strengthen confidence in this early finding. Both patients related the subjective findings at the 4-month to 6-month posttransplant time period, which is what would be expected for development of human fetal rods and cones.

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Postpartum Cerebellar Herniation in von Hippel-Lindau Syndrome
Ihab S. Othmane, MD, Carol Shields, MD, Arun Singh, MD, Jerry Shields, MD, and Warren Goldman, MD

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From the Oncology Service (I.S.O., C.S., J.S., A.S.) and Neurosurgery Department (W.G.), Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania, and the Ophthalmology Department, Kasr El-Amin University Hospital, Cairo University, Cairo, Egypt (I.S.O.). This work was supported by Cairo University Research Foundation Grant, Cairo, Egypt (I.S.O.), the Paul Kayser International Award of Merit in Retina Research, Houston, Texas (J.S.), Eye Tumor Research Foundation, Philadelphia, Pennsylvania, and Macula Foundation, New York, New York (C.S.).

Inquiries to Carol Shields, MD, Oncology Service, Wills Eye Hospital, 900 Walnut St, Philadelphia, PA 19107.