MR Imaging of Fetal Tissue Grafts in the Injured Human Spinal Cord: 2-Year Follow Up

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Introduction

Numerous studies in animal models have demonstrated that grafts of fetal spinal cord (FSC) tissue can provide a partial return of neurological function following spinal cord injury (SCI)[1]. To determine whether this cellular repair strategy can eventually be translated to human patients, a pilot safety and feasibility study was initiated in patients with progressive post-traumatic syringomyelia (PPTS). The initial follow-up with clinical and MRI assessments showed no acute adverse effects due to the transplantation procedure, but the long-term safety of these FSC grafts is still unknown[2]. Thus, we report here the MRI results through two years of follow up in 8 subjects.

Methods

In this non-randomized pilot study, patients were considered for participation if they presented with both clinical and radiological evidence of PPTS, with the syrinx located primarily in the thoracic spinal cord. All subjects received comprehensive assessments, including MRI exam, pre-operatively and at 1.5, 3, 6, 9, 12, 18 and 24 months post-grafting. A total of six males and two females received transplants. The mean age was 53.6 years, and they suffered a SCI between 12 and 31 years (mean: 19 years) prior to grafting. Subjects typically reported that their most severe symptoms were worsening pain, weakness, and spasticity.

Human FSC tissue of 6-9 weeks gestational age was procured following elective abortions and informed consent by the maternal donors. Pieces of donor FSC tissue were then inserted into the syrinx cavities either manually with fine forceps or were slowly injected with a 500µl syringe and 18-gauge cannula. The overlying meninges were then sutured closed, and graft placement was verified by intraoperative ultrasound. The MRI protocol was designed to visualize the entire syrinx in the sagittal plane, and to obtain restricted axial views with higher magnification of the transplant site. Sagittal spin-echo images were acquired with T1- (TR/TE = 600/15 ms), T2- (TR/TE = 2000/90ms), and fluid attenuation by inversion recovery (FLAIR) weighting. Axial slices were obtained with T1-, T2-, and proton-density (TR/TE =3000/15 ms) weighting. All images were acquired with a slice thickness of 3-4 mm and a 256 x 256 matrix size. In-plane resolution was 0.7 x 0.7 mm for axial images, but varied on sagittal images depending upon the field-of-view required to visualize the entire syrinx. Total scan time per subject at each session was approximately 1 hour.

Results

All eight subjects tolerated the operation well and there were no complications related to FSC tissue implantation. Motor and sensory function remained stable in seven subjects, whereas in the remaining case a substantial increase in leg strength and locomotor function was observed. Preoperative MRI scans revealed cysts that ranged in length from 1 cm to 30 cm, and were typically located slightly lateral to the spinal cord epicenter on transverse images. Initial post-operative MRI scans revealed at least partial collapse of the syrinx at the drainage/transplant site in 7 of 8 subjects (Figure 1), whereas distant, non-grafted, sites typically exhibited reaccumulation of CSF. Despite the clear evidence of cyst collapse at the graft sites, no specific boundaries between donor and host tissue were observed on T1- or T2-weighted images. Long-term MRI follow-up through 2 years showed no evidence of delayed hemorrhage, inflammation, or tumorigenicity (i.e., transplant overgrowth) in any subject.

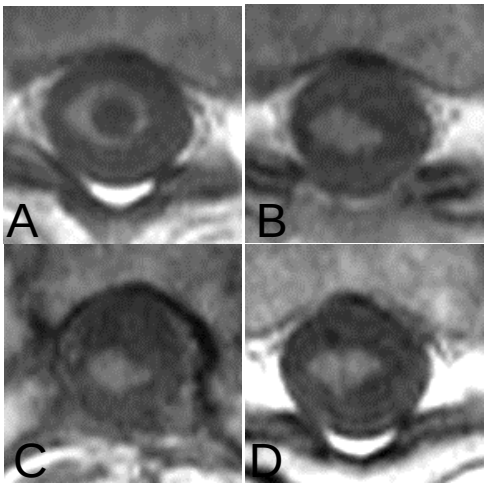

Figure 1: Axial T1-weighted MR images through the graft site in Subject 6 at 2 weeks pre-operative (A), 3 months (B), 12 months (C), and 24 months (D) postgrafting.

Discussion

These results suggest that repeated MRI is a sensitive method for monitoring the response of post-traumatic spinal cord cysts to surgical implantation of neural tissue grafts. In particular, the serial MRI scans of each subject allowed for a more precise comparison between the postoperative evolution of the syrinx and the temporal course of the clinical and neurophysiological outcome measures. Despite the high quality of the images, however, it was still not possible to distinguish specific donor-host boundaries, and thus it was not possible to confirm survival of the FSC grafts with absolute certainty. Therefore, it appears likely that achieving adequate contrast between donor and host tissue will require prelabeling of the donor tissue with a paramagnetic contrast agent[3] or techniques such as diffusion-weighted MRI that could exploit differences in water diffusion anisotropy between FSC tissue and spared white matter in the host spinal cord.

References

1. Anderson,D.K. et al., *Brain Pathol.* **5:**451-457 (1995).
2. Wirth,E.D., III et al., *J. Neurotrauma* **18:**911-929 (2001).
3. Bulte,J.W. et al., *Proc.Natl.Acad.Sci U.S.A* **96:**15256-15261 (1999).

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