MR Guided CED of a Novel Therapeutic for Parkinson's Disease: The Importance of Imaging Feedback

Alastair J Martin[1], Krystof Bankiewicz[2], John Bringas[2], Chad Christine[3], Marin Thompson[2], Janine Beyer[2], and Paul Larson[2]

[1]*Radiology and Biomedical Imaging, UCSF, San Francisco, CA, United States,* [2]*Neurological Surgery, UCSF, San Francisco, CA, United States,* [3]*Neurology, UCSF, San Francisco, CA, United States*

Target Audience: This abstract is aimed at clinicians and researchers that are interested in localized delivery of therapeutics in the brain. It is of particular interest to clinicians that treat Parkinson's disease, researchers developing gene therapies and imaging scientists that are exploring MR guidance for the administration of therapy.

Introduction: Convection enhanced delivery (CED) is a promising approach for delivering therapeutics to the brain. CED bypasses the blood brain barrier and permits volumetric coverage of targeted brain structures. Prior clinical trials that have utilized CED to administer therapeutics have produced disappointing outcomes and technical limitations in the administration of the therapy are considered to be a significant contributing factor to these failures. We are performing a phase I safety study that utilizes an optimized delivery platform and MR guidance to administer a promising gene therapy agent (AAV2-hAADC) in patients with Parkinson's disease. This therapeutic assists in the conversion of levodopa to dopamine and therefore produces more effective response to Sinemet, the levodopa based drug used in the treatment of Parkinson's disease. Since dopaminergic deficiency in Parkinsonian patients is most pronounced in the putamen, this is the preferred target structure for AAV2-hAADC therapy. In this study we evaluate the use of MR imaging feedback to determine whether CED infusions are achieving their desired target coverage.

Methods: All patients were consented under a protocol approved by our institutional committee on human research. Patients were brought to the MR suite and underwent MR imaging to delineate the putamen and select preferred infusion sites. A burrhole was created at the desired entry site and an MR compatible trajectory guide (ClearPoint, MRI Interventions, Irvine, CA) affixed to the skull. The trajectory guide was oriented under real-time imaging to be directed to the selected targets within the putamen and a 16-gauge stepped infusion cannula inserted. The vector solution was mixed with an MR contrast agent (Prohance to 1mM final) to enhance CED infused regions and a ramped infusion rate paradigm was employed. At each new cannula location infusion rates began at 1µl/min and were ramped up as high as 10µl/min. Continuous MP-RAGE imaging (3 min) with isotropic 1mm voxels was performed to monitor the infusion.

Results: All patients successfully underwent bilateral infusion of the putamen. In order to improve coverage, anterior and posterior putamen infusions were performed for a total of four infusions per patient. CED infusion progress was successfully monitored with MR imaging and acceptable coverage of the putamen was achieved in all cases. However, several factors that led to non-ideal CED infusions were identified. The stepped cannula limited backflow but this remains a challenge for CED infusions (*Figure 1*). Notably, when brain shift was ongoing during CED infusions, the effectiveness of the seal between the cannula and brain was compromised. Surrounding anatomical structures, including vascular and CSF spaces, also could lead to non-ideal coverage of the putamen (*Figure 2*). Detection of non-ideal CED infusions permitted real time adjustment to infusion strategy, including changing cannula depth and aborting ineffective infusions.

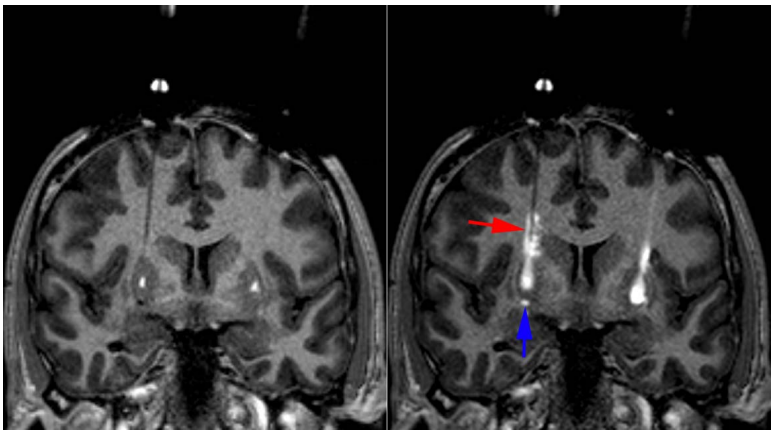

Figure 1: Bilateral infusion of the putamen is shown in coronal planes at the start of infusion (left) and near completion (right). The infusion cannulae are well positioned within the center of the putamen. As the infusion evolves evidence of reflux is evident.

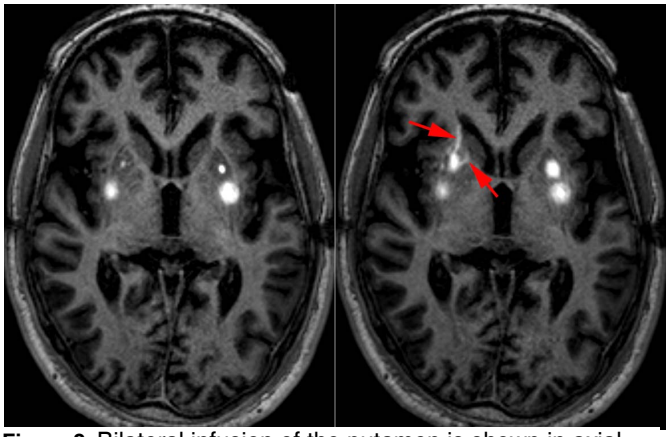

Figure 2: Bilateral infusion of the putamen is shown in axial planes at the start of anterior infusions (left) and near completion (right). Shunting via vascular channels can be appreciated on the subject's right side (arrows).

Conclusions: CED administration into the putamen of Parkinson's patients frequently deviates from the intended coverage. Real time imaging feedback is crucial to detect when non-ideal distributions occur in order to allow for corrective measures or the termination of an ineffective infusion.