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Real-time MRI-guided delivery of AAV2-AADC gene therapy for parkinson's disease and AADC deficiency in children

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Gene transfer technology can correct genetic mutations in the brain. Neuro gene delivery via direct intrapranchymal injections of Adeno-Associated Viral (AAV) vectors is a locally administered treatment that requires accurate delivery to maximize safety and efficacy. Gene therapy using Adeno-Associated Virus (AAV2) carrying the Amino Acid Decarboxylase (AADC) gene has the potential to improve the clinical response to levodopa when infused into the putamen of Parkinson's Disease patients (PD) or to generate dopamine production in children with AADC gene mutation after direct administration to substantia nigra and ventral tegmental area. Prior clinical trials have shown possible benefit but may have been limited by inadequate anatomical vector delivery or off-target vector distribution. Using intraoperative MRI and co-infusing the vector with gadoteridol now allows real-time visualization of infusions. Analysis of bilateral MRI-guided putaminal infusions for 15 Parkinsonian patients and 3 children with AADC deficiency in an ongoing Phase Ib/2 AAV2-AADC clinical trial was performed. T1-weighed images were used to calculate coverage of the putamen. The infusion strategy evolved during the trial to maximize coverage of the putamen by modifying the cannula design, increasing the infusion volumes and altering the cannula trajectories. Real-time MRI-guided delivery allows various infusion strategies to be employed to maximize target coverage. MR-guided infusions of the vector into the midbrain of AADC-deficient children resulted in 100% coverage of target structures. In both PD and AADC deficient children AAV-AADC gene transfer was able to significantly increase clinical outcome as manifested by 4 hours increase in ON time in PD patients at 12 months and increase of motor performance in AADC-deficient children. In addition, significant reduction of oculomotor crises was observed as well. These results show that advances in surgical techniques have markedly improved vector delivery and that AAV2-AADC has strong therapeutic potential in both indications presented here.

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