Real-time MR-guided 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/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 patients (PD) or to generate dopamine production in children with AADC gene mutation after administration to substantia nigra and ventral tegmental area. Neurotrophic factors hold great promise in treatment of PD. 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 allows real-time visualization of infusions. The infusion strategy evolved during the trial to maximize anatomical coverage. Analysis of bilateral MR-guided putaminal infusions of over 30 PD patients and 3 children with AADC deficiency in ongoing Phase Ib/2 clinical trials were performed. In both PD and AADC deficient children AADC gene transfer significantly increased clinical outcome as manifested by 4 hrs. increases in ON time in PD patients at 12 months and increase of motor performance and reduction or elimination of oculomotor crises in AADC-deficient children. PET with (18FDOPA) detected expression (AADC trials) and effects of gene therapy (GDNF). 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.