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Breakthrough news in adenoviral vector-mediated AADC gene therapy: Lessons from the success in AADC deficiency and possible future applications

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Aromatic L-amino acid decarboxylase (AADC) is crucial in catecholaminergic-serotoninergic neurotransmission, which regulates voluntary movement, cognition, emotion, and autonomic processing.[1] AADC converts 5-hydroxytryptophan and L-DOPA into serotonin and dopamine, respectively. In turn, dopamine is the precursor of norepinephrine and epinephrine.[1] Biallelic variants in the dopa decarboxylase gene (*DDC*) causes AADC deficiency (AADC-def), a neurometabolic disorder featuring hypotonia, oculogyric crises (OGC), developmental delay, and mood, sleep and autonomic disturbances.[1] Brain AADC activity depletion also occurs in Parkinson's disease (PD) following dopaminergic neuron degeneration in substantia nigra pars compacta (SNpc).[1,2]

In parallel with AADC-def research, AADC gene therapy has been explored in PD preclinical and phase I/I-II trials for two decades, with the rationale to augment L-DOPA-to-dopamine conversion.[2,3] Direct transfection of striatal/putaminal neurons with an adenoviral vector carrying human *DDC* (AAV2-hADDC) induces sustained gene expression and dopamine synthesis.[2] While exogenous L-DOPA ignites this process in PD, endogenous L-DOPA is intrinsically abundant in AADC-def. Since the first clinical trial, 31 PD and 20 AADC-def patients received intrastriatal/intraputaminal AAV2-hADDC infusion, which is deemed safe and effective.[1,2]

Pearson and colleagues[4] first investigated AAV2-hADDC delivery to midbrain regions (i.e., SNpc and ventral tegmental area) in seven AADC-def cases. Unlike PD, AADC-def is characterized by intact midbrain dopaminergic neurons (including their efferent projections), and anterograde axonal transport to downstream brain structures (e.g., striatum) is therefore preserved. The authors postulated that midbrain AAV2-hADDC delivery rescued dopamine synthesis in a wider neural network encompassing nigrostriatal, mesolimbic, and mesocortical pathways, thus ultimately addressing autonomic and affective AADC-def manifestations.[4] A novel real-time, MRI-guided, convection-enhanced delivery system (RT-MRI-CED) ensured intraoperative confirmation of catheter placement, continuous monitoring of vector infusion, and enhanced "on-target" infusate distribution. Trial procedure was proven safe and effective in restoring brain AADC activity. Post-operative PET documented appearance of midbrain and striatal 6-[^{18}F]-fluoro-L-DOPA uptake, which was absent at baseline due to defective AADC. Furthermore, after the procedure, CSF homovanillic acid significantly raised, confirming increased dopamine metabolism,[4] whereas 5-hydroxyindolacetic and 3-O-methyldopa remained unchanged, which is consistent with exclusion of serotoninergic nuclei and incomplete AADC restoration, respectively.[4] The

latter suggests that localization rather than magnitude of rescued AADC function may be crucial for clinical improvement.[4] Specifically, 6/7 cases achieved OCG remission, 6/7 head control at 12 months, and 6/7 and 2/7 independent sitting and walking at 24 months, respectively. Caregiver diaries documented improvement of behavioral, sleep, and autonomic symptoms. In all cases, irritability, insomnia, and dyskinesia transiently exacerbated within one month after surgery, reflecting abrupt increase in dopamine levels.[4]

By targeting new anatomical regions and optimizing the procedure, Pearson and coworkers[4] provides an advanced proof-of-concept disease-modifying strategy to support randomized clinic trials for AADC-def. In keeping with their refined procedure, RT-MRI-CED-guided AAV2-hADDC infusion recently achieved improvement of UPDRS-III "on"-medication score in PD patients, likely due to maximized putaminal infusate coverage compared to previous studies.[5] In conclusion, besides therapeutic implications for AADC-def, this study paves the way for designing robust clinical trials investigating AAV2-hADDC as pathomechanism-oriented and possibly long-term treatment for PD, as well as RT-MRI-CED-guided adenoviral vector-mediated gene therapy for other neurometabolic disorders.

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Author Roles

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3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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Ethical Compliance Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approvoal of an institutional review board and patient consent were not required for this work.

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