Aromatic L-amino acid decarboxylase deficiency

The autosomal recessive defect of aromatic L-amino acid decarboxylase (AADC) leads to a severe neurological disorder with manifestation in infancy due to a pronounced, combined deficiency of dopamine, serotonin and catecholamines. The success of conventional drug treatment is very limited, especially in patients with a severe phenotype. The development of an intracerebral AAV2-based gene delivery targeting the putamen or substantia nigra started more than 10 years ago. Recently, the putaminally-delivered construct, Eladocagene exuparvovec has been approved by the European Medicines Agency and by the British Medicines and Healthcare products Regulatory Agency. This now available gene therapy provides for the first time also for AADC deficiency (AADCD) a causal therapy, leading this disorder into a new therapeutic era.

Method: By using a standardized Delphi approach members of the International Working Group on Neurotransmitter related Disorders (iNTD) developed structural requirements and recommendations for the preparation, management and follow-up of AADC deficiency patients who undergo gene therapy.

Discussion: This statement underlines the necessity of a framework for a quality-assured application of AADCD gene therapy including Eladocagene exuparvovec. Treatment requires prehospital, inpatient and posthospital care by a multidisciplinary team in a specialized and qualified therapy center. Due to lack of data on long-term outcomes and the comparative efficacy of alternative stereotactic procedures and brain target sites, a structured follow-up plan and systematic documentation of outcomes in a suitable, industry-independent registry study are necessary [1].

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Roubertie A, Opladen T, Brennenstuhl H, Hübschmann OK, Flint L, Willemsen MA, Leuzzi V, Cazorla AG, Kurian MA, François-Heude MC, Hwu P, Ben Zeev B, Kiening K, Roujeau T, Pons R, Pearson TS. Gene therapy for aromatic L-amino acid decarboxylase deficiency: requirements for safe application and knowledge-generating follow-up. J Inherit Metab Dis. 2023 Jul 4. doi: 10.1002/jimd.12649. Epub ahead of print. PMID: 37402126.