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Neurology and Neuroscience

Fast Facts Information Sheets

Aromatic L-Amino Acid Decarboxylase Deficiency

HEALTHCARE

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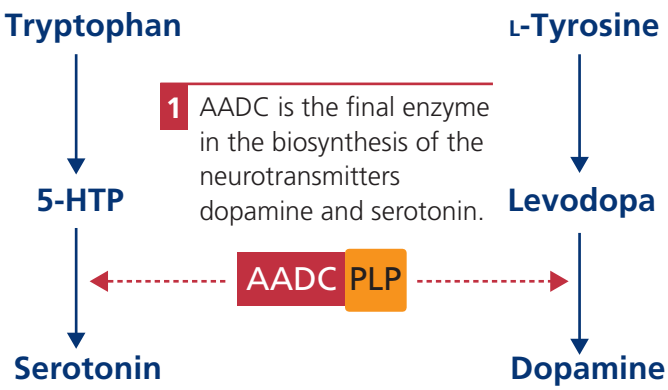
Aromatic L-Amino Acid Decarboxylase Deficiency

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare, inherited, non-progressive neurological disorder that typically manifests in the first year of life. Most patients have a severe, sometimes life-threatening, phenotype.

Epidemiology

- 350 cases reported in the literature worldwide[1]
- Estimated prevalences:[2]
  - USA: 1 in 90 000
  - Europe: 1 in 116 000
  - Japan: 1 in 162 000
- Affects all races and ethnicities, but most prevalent in Taiwanese, Chinese, and Japanese individuals due to a common founder pathogenic variant in the *DDC* gene (c.714+4A>T [IVS6+4A>T])



1 AADC is the final enzyme in the biosynthesis of the neurotransmitters dopamine and serotonin.

Etiology

- Autosomal recessive inheritance
- >50 pathogenic variants (mostly missense variants) in the *DDC* gene, which encodes the AADC enzyme
- *DDC* gene is located at 7p.12.1-12.3
- Pathogenic variants affect AADC in three ways:
  - Reduce catalytic enzyme activity
  - Reduce the binding capacity of the co-factor pyridoxal 5'-phosphate (PLP)
  - Cause a defect in protein folding

2 Without the enzymatic activity of AADC, levodopa accumulates and is converted to 3-*O*-methyldopa (3-OMD) by a methylation pathway.

3-*O*-methyldopa

3 3-OMD has been found to be a reliable marker of AADC deficiency in dried blood spot testing for newborn screening.[3]

Clinical presentation

In most cases, AADC deficiency may be suspected from key signs and symptoms soon after birth. Most patients have a severe phenotype, comprising some or all of the following.

- Axial muscular hypotonia
- Dystonia
- Oculogyric crises (OGC)
- Excessive crying
- Gastrointestinal symptoms (gastroesophageal reflux, diarrhea, constipation)
- Feeding difficulties
- Autonomic dysfunction (excessive sweating, arterial hypotension, bradycardia, temperature instability, ptosis, nasal congestion)
- Global developmental delay
- Restricted growth
- Sleep disturbances
- Behavioral/emotional problems
- Intermittent hypoglycemia
- Epileptic seizures

Confirming the diagnosis

Genetic and/or laboratory testing can confirm the diagnosis.[4]

Two of the following three criteria must be present:

- Abnormal pattern of cerebrospinal fluid metabolites related to AADC deficiency
  - Reduced dopamine and serotonin degradation products (5-hydroxyindoleacetic acid, homovanillic acid, 3-methoxy-4-hydroxyphenylglycol)
  - Normal levels of pterins (neopterin, biopterin)
  - Elevated levels of 3-OMD, levodopa, and 5-hydroxytryptophan (5-HTP)
- Decreased AADC enzymatic plasma activity
- Compound heterozygous or homozygous pathogenic variants in the *DDC* gene

1. Himmelreich N et al. *Mol Genet Metab*. 2023;139(3):107624.
2. Himmelreich N et al. *Mol Genet Metab*. 2021;134(1-2):216.
3. Chien YH et al. *Mol Genet Metab*. 2016;118(4):259-263.
4. Wassenberg T et al. *Orphanet J Rare Dis*. 2017;12(1):12.

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Management of AADC deficiency

The combination and severity of symptoms differs for each patient. Treatment must be tailored to the individual's needs and frequently adapted throughout the disease course.[4]

First-line treatment focuses on the dopaminergic and/or serotonergic deficiency.

A combination of medications is introduced sequentially and titrated progressively to the desired target dose.

- Pyridoxine (vitamin B6)
- Selective dopamine agonists (DA): pramipexole (base), ropinirole, rotigotine (transdermal), bromocriptine
- Monoamine oxidase inhibitors (MAOI): selegiline, tranylcypromine

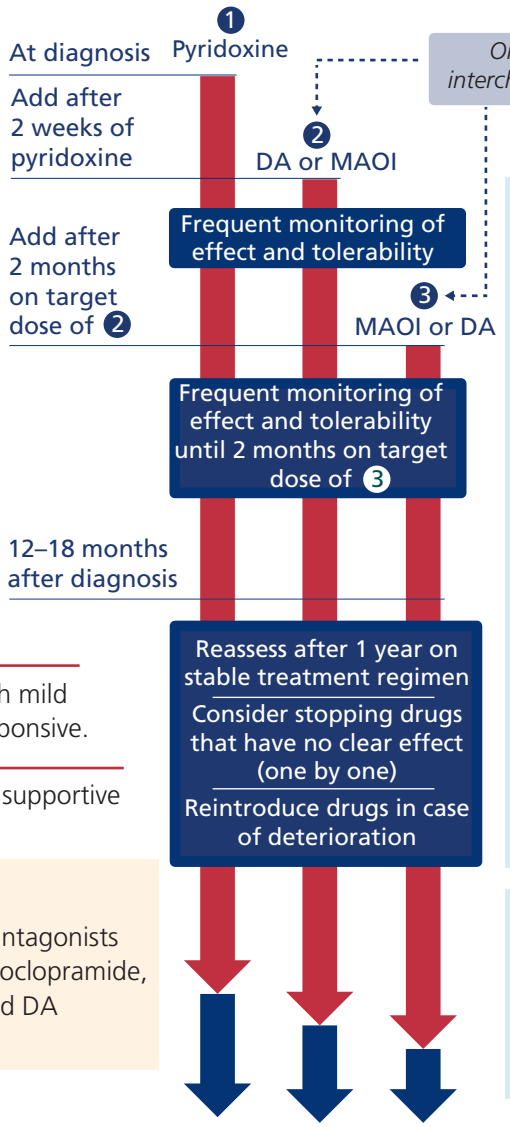
Most of these drugs are not approved by international drug authorities for AADC deficiency or for patients under 15 years old.

Only a small proportion of patients with mild forms of AADC deficiency are drug responsive.

Additional symptomatic treatment and supportive care is given as required.

Drugs to be avoided include catecholaminergic or serotonergic antagonists (e.g. haloperidol, tetrabenazine, metoclopramide, levomepromazine) and ergot-derived DA (e.g. pergolide, cabergoline).

First-line treatment



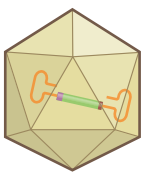
Additional symptomatic treatment

Symptom	
Nasal congestion	α-agonists nose drops
Autonomic symptoms	Anti-cholinergics
Dystonia/ OGC	Anti-cholinergics
Sleep problems	Melatonin/ clonidine

Assess effect and tolerability
Discontinue if not effective/intolerable side effects

Supportive care

Tube feeding; monitoring for gastrointestinal, cardiac, respiratory, and orthopedic problems; pain treatment; infection control; physical rehabilitation; psychosocial support



Gene therapy

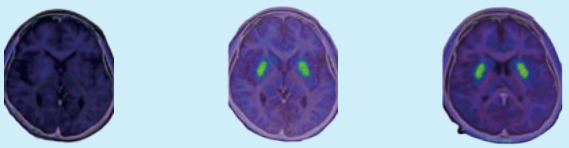
Adeno-associated virus (AAV)-mediated gene therapy can be administered directly to the brain. Eladocagene exuparvovec, a recombinant AAV2 vector containing the human *DDC* gene, is the first approved gene therapy in Europe and the UK for the treatment of adults and children (18 months and older) with AADC deficiency. It is delivered intraputaminally by stereotactic surgery.

Clinical trials of AAV gene therapy in patients with AADC deficiency in Taiwan,[5] Japan,[6] Europe,[7] and the USA[8] have shown:

- Increased dopamine production
- Improvements in motor function
- Reduction in non-motor symptoms

AAV gene therapy does not provide a cure for AADC deficiency, and the long-term complications and outcomes are unknown.

Parents must be provided with information about the potential risks and benefits of gene therapy to provide informed consent.



Before gene therapy | 6 months after gene therapy | 5 years after gene therapy

In the Japan trial, PET high signal intensity in the bilateral putamen 5 years after gene therapy indicates sustained AADC activity and expression.

5. Tai CH et al. *Mol Ther.* 2022;30(2):509-518.
6. Kojima K et al. *Brain*. 2019;142(2):322-333.
7. François-Heude MC et al. *Mov Disord Clin Pract*. 2023;10(5):811-818.
8. Pearson TS et al. *Nat Commun*. 2021;12(1):4252.

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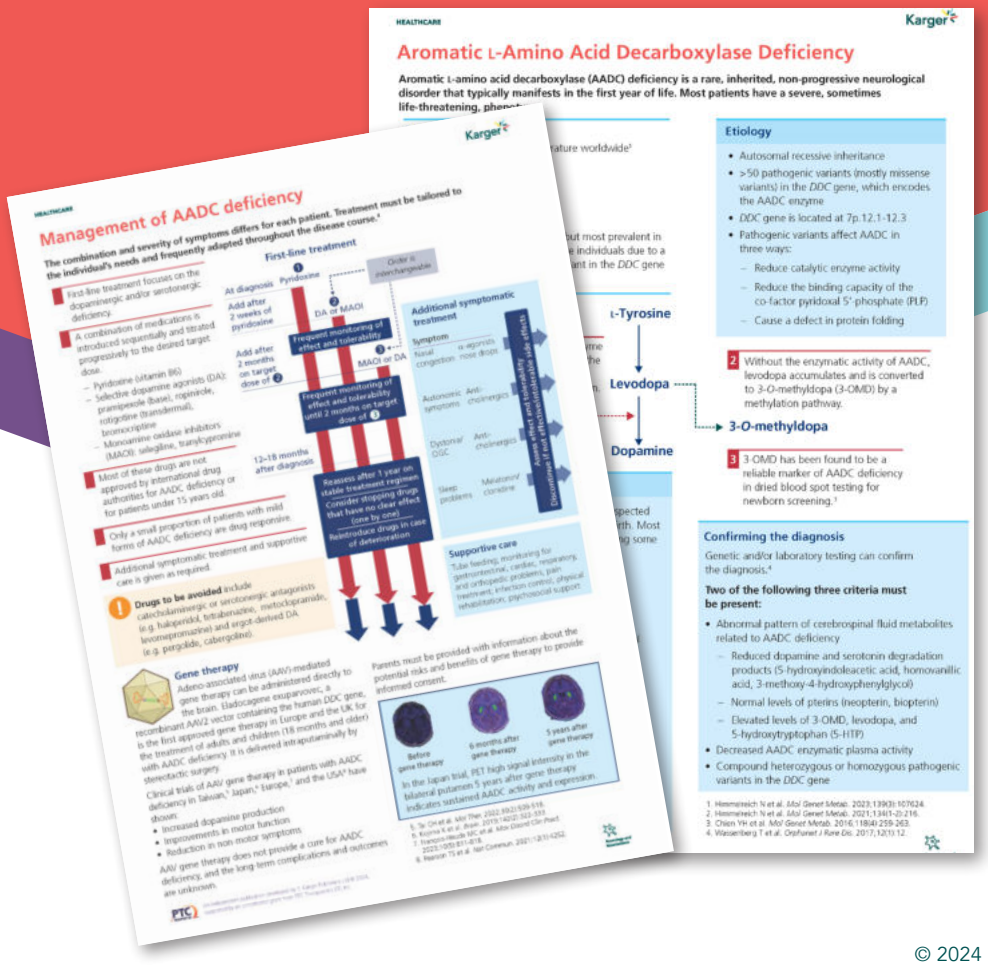

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