

Aromatic-L-amino acid decarboxylase (AADC) deficiency: What is it and how is it diagnosed?

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AADC deficiency is a severe disease

AADC deficiency typically presents early and can lead to the need for lifelong care, with life-limiting motor and autonomic dysfunction, developmental delay leading to premature death.¹⁻⁴

Patients usually do not develop full head control or the ability to sit unassisted or stand.

AADC deficiency affects patients of any gender, ethnic origin or geographical region.



AADC is an enzyme required for biosynthesis of dopamine and serotonin. AADC deficiency has a wide range of symptoms.

AADC is an enzyme required for biosynthesis of dopamine and serotonin^{2,3,6,7}

- In the autosomal recessive disease AADC deficiency, mutations in the dopa decarboxylase (DDC) gene result in reduced AADC enzyme activity, leading to severe combined deficiency of the neurotransmitters dopamine, serotonin, norepinephrine, and epinephrine
- The result is an increase in L-dopa, 3-OMD,

AADC deficiency can manifest with a broad spectrum of symptoms. The most common are¹⁻³:



- In the published consensus guidelines:
- Mean age of onset for patients with AADC deficiency was 2.7 months (n=68)²



patient

patient 2

VLA, and 5-HTP, and a decrease in the neurotransmitter metabolites HVA and 5-HIAA



Despite this young age of symptom onset, the mean age of diagnosis was 3.5 years (n=68)²

In a natural history study of 37 patients diagnosed with AADC deficiency, 97% failed to achieve motor milestones^{1,5}

This includes the ability to sit, stand, walk, run, and/or speak Symptoms typically do not improve, leading to the need for lifelong care^{1,3}

- Patients who live to adulthood suffer long-term cardiac and orthopedic complications and increased risk of infections²
- Body weight may be normal in the first few months, but growth and weight gain can slow after the first year⁵

AADC deficiency can affect patients of any gender, ethnic origin, or geographic region^{2,5}

ADC deficiency has been reported in individuals of Asian, Caucasian, Arabic, Iranian, and Jewish ethnic origin^{2,a}

Images courtesy of Dr. Muramatsu, Department of Pediatrics, Jichi Medical University, Japan





Oculogyric crisis^{2,3,6,8}

Episodes of sustained upward or lateral deviation of the eyes, rhythmic orofacial movements, backward and lateral flexions of the neck, tongue protrusion, and jaw spasms



Can last a few seconds or persist for several hours, and occur several times per day or week May not be present in all cases

Others^{2,3}

Hypokinesia (32%) Dystonia (53%)

Autonomic symptoms^{2,3,6}

■ Hyperhidrosis (65%) ■ Ptosis (39%) ■ Hypersalivation (41%) ■ Nasal Congestion (31%) ^aPercentages based on a clinical study of 78 patients diagnosed with AADC deficiency.³

Many of the most common symptoms of AADC deficiency can also be attributed to a number of other conditions such as cerebral palsy and epilepsy, resulting in potential misdiagnosis.^{2,3,9-11} However, the presence of the following should prompt investigation of AADC deficiency:

- Autonomic symptoms that are not typical of other conditions^{2,8-11}
- Normal EEG and neuroimaging; one study showed that only a small proportion of patients with AADC Deficiency had an abnormal EEG, MRI, or CT³
- Kojima K et al, Gene therapy improves motor and mental function of aromatic L-amino acid decarboxylase deficiency, Brain 2019: 142;322-333.
- 5. Hwu WL, Chien YH, Lee NC, et al. JIMD Rep. 2018;40:1-6. doi: 10.1007/8904_2017_54.
- 6. Pons R, Ford B, Chiriboga CA, et al. Neurology. 2004;62(7):1058-1065.
- 7. Hwu WL, Lee NC, Chien YH, et al. Adv Pharmacol. 2013;68:273-284.
- Lee WT. Epilepsy & Seizure. 2010;3(1):147-153. https://www.jstage. jst.go.jp/article /eands/3/1/3_1_147/_article/-char/en. Accessed December 18, 2018.
- 9. Krigger KW. Am Fam Physician. 2006;73(1):91-100.
- 10. Ng J, Papandreou A, Heales SJ, et al. Nat Rev Neurol. 2015; 11(10):567-584.
- 11. Kurian MA, Dale RC. Continuum (Minneap Minn). 2016;22(4 Movement Disorders):1159-1185.
- 12. Garcia-Cazorla A, Duarte S, Serrano M, et al. Mitochondrion. 2008;8(3):273-278.
- 13. Helman G, Pappa MB, Pearl PL. JIMD Rep. 2014;17:23-27.

Earlier identification of AADC deficiency can help improve the care and management of patients

The diagnostic pathway for suspected AADC deficiency^{2,12}



Following this diagnostic process can help diagnose AADC deficiency²

Perform²

CSF neurotransmitter

Other diagnostic tests that may be helpful²

Blood level measurement of 3-OMD

Urinary organic acid analysis

CONCLUSIONS

AADC deficiency is a rare and devastating disorder of the central nervous system that typically presents early and may require

Autonomic symptoms are often present Ptosis
Temperature Instability
Nasal Congestion

- metabolite panel
- Plasma enzyme activity assay

Interpret² $\mathbf{2}$

- Reduced HVA, 5-HIAA, and MHPG; elevated 3-OMD, L-dopa, and 5-HTP; and normal pterins in CSF
- Confirm with genetic testing²
 - Mutation(s) in the DDC gene

Blood plasma	CSF	Genetic testing
Decreased AADC enzyme activity	HIGH LEVELS OF	Variants in DDC gene
	3-OMD, L-dopa, 5-HTP	
	✓ LOW LEVELS OF	
	5-HIAA, HVA	
	Normal pterins	

CSF=cerebrospinal fluid; MHPG=3-methoxy-4-hydroxyphenylglycol.

Low plasma AADC AND/OR enzyme activity

Consensus guidelines

with a genetic test²

recommend confirming an

AADC deficiency diagnosis

Increased urinary VLA

lifelong care^{1-3,13}. It can cause hypotonia, developmental delay, movement disorders and autonomic symptoms²⁻⁷

Earlier identification can help improve the care and management of patients with AADC deficiency¹⁻³. However, AADC deficiency may be misdiagnosed or undiagnosed^{2,8}.

Hypotonia is the most commonly reported symptom of AADC deficiency. It is therefore necessary to consider testing for AADC deficiency in patients with unexplained hypotonia.

Poster 104 – Theme 3: Share, Care, Rare: Transforming care for rare diseases by 2030