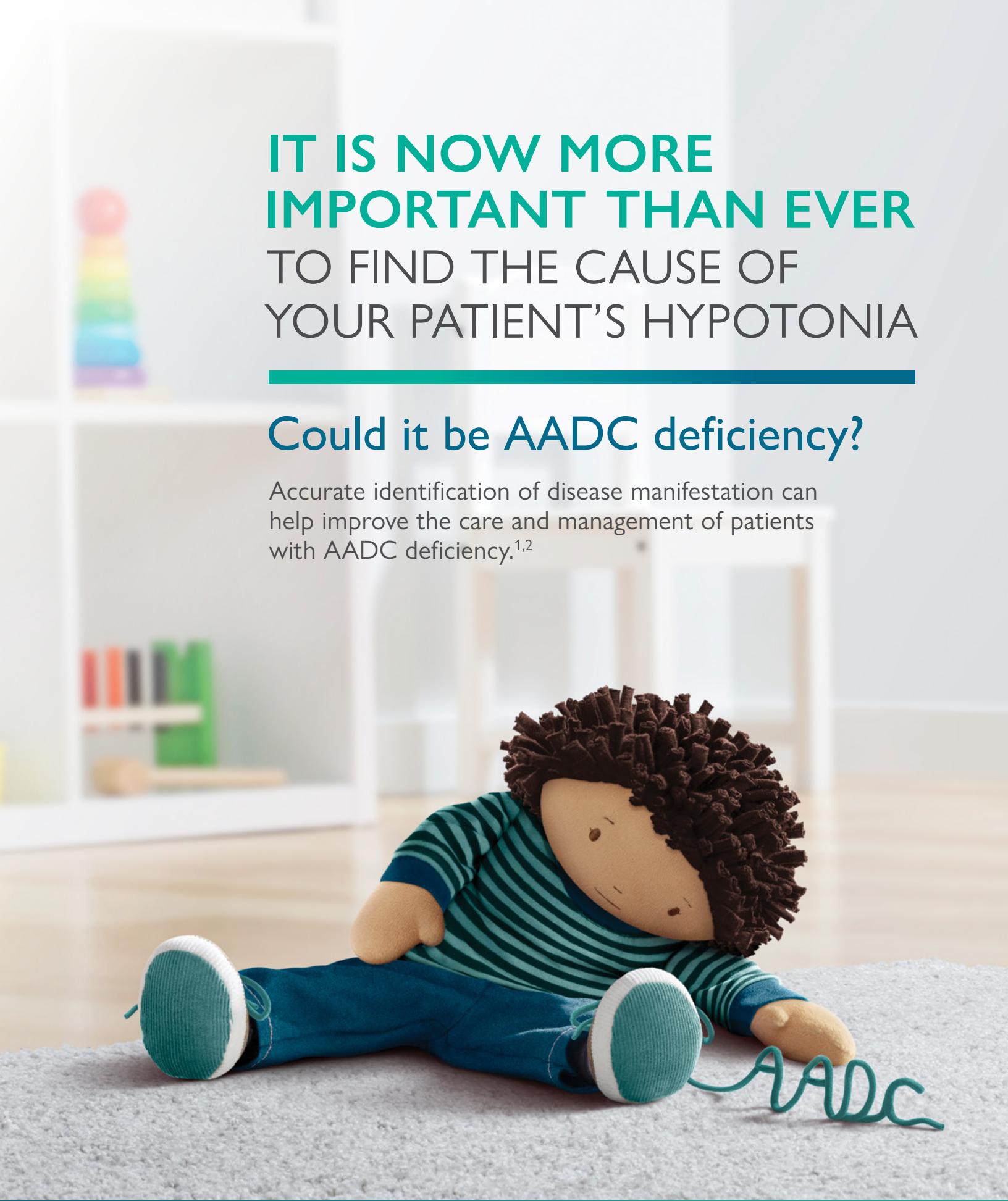
IT IS NOW MORE IMPORTANT THAN EVER TO FIND THE CAUSE OF YOUR PATIENT'S HYPOTONIA

Could it be AADC deficiency?

Accurate identification of disease manifestation can help improve the care and management of patients with AADC deficiency.[1,2]



Neurotransmitter disorders are increasingly recognized as an expanding group of inherited neurometabolic syndromes that affect children

Neurotransmitters, like dopamine, support a variety of functions in the body, including cognition, emotion, and movement. Dopamine is specifically involved with decision-making, motivation, and motor control.[3-5] Within a growing group of genetic conditions referred to broadly as neurotransmitter disorders, many are marked by a disruption in monoamine neurotransmitter synthesis, metabolism, and homeostasis.

Neurotransmitter deficiency can lead to a range of neurological manifestations in childhood, including[3,6]:

- Developmental delay
- Epilepsy
- Neuropsychiatric features
- Motor disorders
- Autonomic dysfunction

One neurotransmitter disorder is Aromatic L-amino Acid Decarboxylase (AADC) deficiency, which is a genetic disease associated with defects in neurotransmitter synthesis that can lead to a manifestation of a broad spectrum of symptoms.

The most common symptoms of this autosomal recessive disorder are[7-10]:

- Hypotonia
- Developmental delay
- Movement disorders, especially oculogyric crises

Many of the most common symptoms of AADC deficiency can also be attributed to a number of other conditions, resulting in potential misdiagnosis.[3,6-8,11-14]

Some of these conditions include:

- Cerebral palsy
- Epilepsy
- Juvenile parkinsonism

"If all of these symptoms are observed, the diagnosis can be made. But, if you have no experience or knowledge about it, you may have difficulty making a diagnosis."

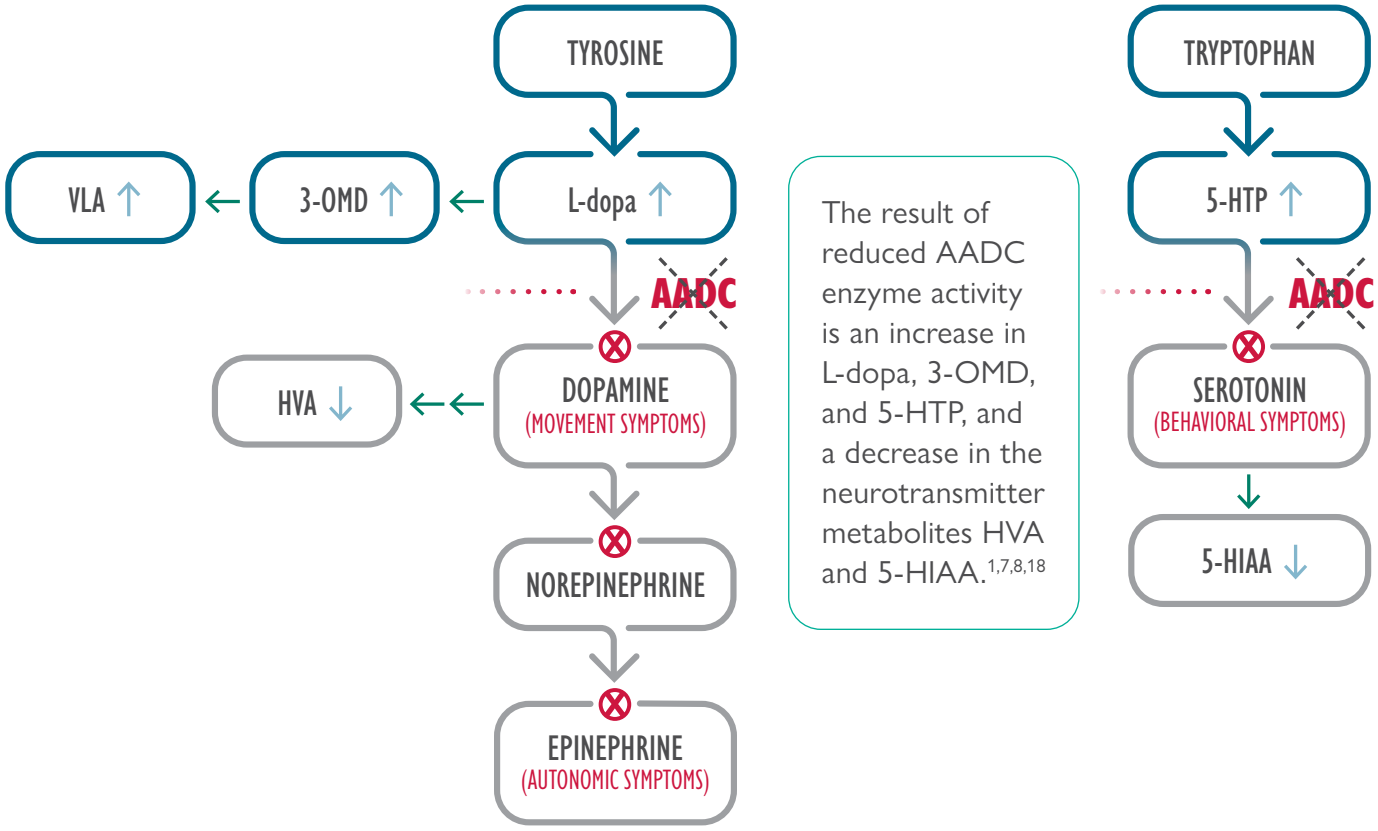
Takanori Yamagata, MD
Department of Pediatrics, Jichi Medical University, Shimotsuke, Tochigi, Japan

View videos to hear more about symptoms of AADC deficiency

Unlike juvenile parkinsonism and certain forms of epilepsy, AADC deficiency is not neurodegenerative or multifactorial.[4,7,11,15-17]

AADC is an enzyme required for biosynthesis of dopamine and serotonin[7]

In AADC deficiency, mutations in the dopa decarboxylase (*DDC*) gene result in significant reduction or complete loss of AADC enzyme activity, leading to severe combined deficiency of dopamine, serotonin, norepinephrine, and epinephrine.[1,7,8,18]



The result of reduced AADC enzyme activity is an increase in L-dopa, 3-OMD, and 5-HTP, and a decrease in the neurotransmitter metabolites HVA and 5-HIAA.[1,7,8,18]

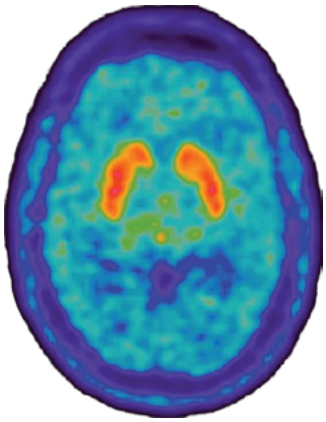
Adapted from Wassenberg 2017.[7]

Visit **AADCInsights.com** to learn more about AADC deficiency and how to identify patients who may have this neurotransmitter disorder.

3-OMD=3-O-methyldopa; 5-HIAA=5-hydroxyindoleacetic acid; 5-HTP=5-hydroxytryptophan; HVA=homovanillic acid; L-dopa=L-3,4-dihydroxyphenylalanine; VLA=vanillactic acid.

The putamen is a major site of dopamine activity and plays a critical role in motor function[19,20]

The putamen is part of the dorsal striatum, which plays a key role in corticostriatal connections that determine motor performance. It is a major site of AADC enzyme activity, and, consequently, dopamine activity.[4,19,21]

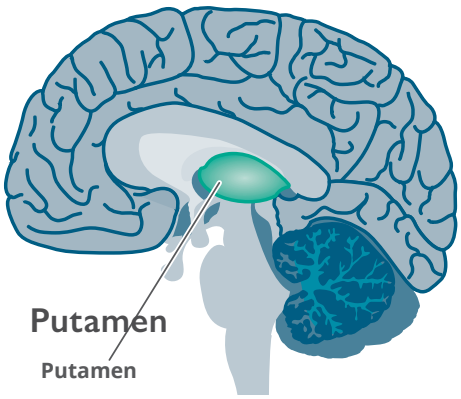


Axial brain image of ^{18}F-DOPA PET showing striatal uptake in both caudate and putamen nuclei

As an important site of dopamine signaling, a deficiency of dopamine in the putamen can lead to dopamine depletion and motor dysfunction in patients with AADC deficiency.[4,20]

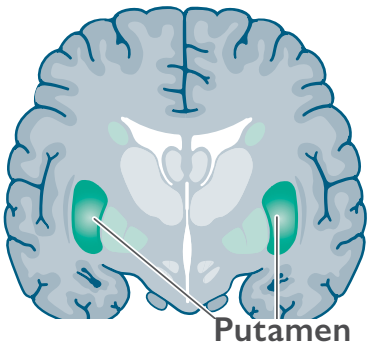
SAGITTAL SECTION

SAGITTAL SECTION



CORONAL SECTION

CORONAL SECTION

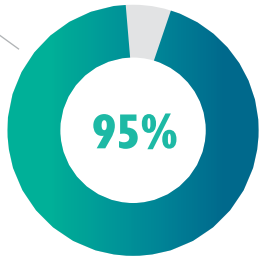


Recognize the signs and symptoms of AADC deficiency

In a clinical study of 78 patients who were diagnosed with AADC deficiency, the following symptoms were documented[8]:

Hypotonia[8]

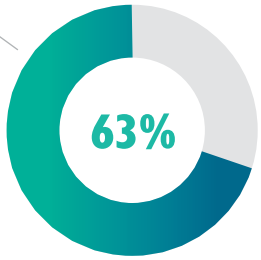
- Most commonly reported symptom



n=74

Developmental delay[8]

- In AADC deficiency, developmental delay may include impairments in head control, crawling, or standing, and speech delays[7,10]

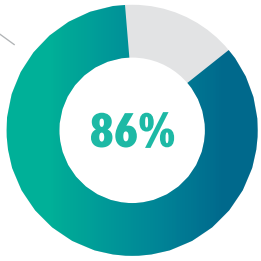


n=49

Movement disorders

Oculogyric crisis[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[18]
- Can last a few seconds or persist for several hours, and occur several times per day or week[1]
- May not be present in all cases[8]
- Often misdiagnosed as a seizure, epilepsy, or mitochondrial disease[1,22]



n=67

Other movement disorders or symptoms include[8]:

- Dystonia (53%) n=41
- Hypertonia (44%) n=35
- Hypokinesia (32%) n=25

Autonomic symptoms include[8]:

- Hyperhidrosis (65%) n=51
- Hypersalivation (41%) n=32
- Ptosis (39%) n=30
- Nasal congestion (31%) n=24

"A lot of these manifestations are non-specific, and one needs to synthesize them and put them together to arrive at the correct diagnosis of AADC deficiency."

Phillip Pearl, MD
Director, Epilepsy and Clinical Neurophysiology at Boston Children's Hospital; William G Lennox Chair and Professor of Neurology at Harvard Medical School, Boston, MA

View this video to hear more from this interview ›

Visit **AADCInsights.com** to review signs and symptoms documented in patient cases.

AADC deficiency may be misdiagnosed or go undiagnosed, delaying treatment and proper management[2,7,8]

Despite symptom onset during infancy, diagnosis is typically delayed[7]:

3.5 Mean age of diagnosis
3.5 years

Age range of diagnosis
2 months to 23 years

Symptoms of neurotransmitter disorders can overlap with those of other neurological disorders, which can make diagnosis challenging. 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.[3,6-8,12-14]

The challenge of a correct diagnosis: conditions with symptoms similar to those of AADC deficiency

AADC deficiency symptoms[2,7]	May be diagnosed as[3,11,12,14,22]
Oculogyric Crises	Epilepsy
Dystonia • Rigidity • Motor Delay	Cerebral Palsy
Dystonia • Developmental Delay • Rigidity	Juvenile Parkinsonism
Hypotonia • Akinesia • Ptosis	Neuromuscular Disorders

Both juvenile parkinsonism and AADC deficiency are associated with a deficiency in dopamine, but they differ in etiology and presentation. Unlike juvenile parkinsonism, **AADC deficiency is a nonprogressive, neurodevelopmental, single-gene disorder with symptom onset during infancy.**[4,7,11,16]

You may want to consider an alternate diagnosis of a neurotransmitter disorder such as AADC deficiency for your patients with:

- Cerebral palsy of unknown etiology
- Epilepsy that is refractory to treatment
- Juvenile parkinsonism whose symptoms don't progress

Look for key differentiating signs and symptoms of AADC deficiency

One or a combination of the following red-flag diagnostic clues should prompt investigation for a neurotransmitter disorder, including AADC deficiency:

Oculogyric crises[2,8,23]

- 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 that can sometimes be confused with seizures[13,18]

EEG or neuroimaging inconsistent with symptoms

- One study showed that only a small proportion of patients with AADC deficiency had an abnormal EEG, MRI, or CT[8]

Autonomic symptoms[2]

- Multiple signs of autonomic dysfunction[13]

Diurnal variation[3,7,24]

- Symptoms become exacerbated or more prominent late in the day and improve with sleep[3,24]

"If a physician is thinking AADC and trying to decide whether it might be a primary seizure disorder or cerebral palsy, if they look at the autonomic problems and they're there in that child, that will move them away from the seizure diagnosis or cerebral palsy diagnosis."

Keith Hyland, PhD
Strategic Director, Medical Neurogenetics Laboratories – A LabCorp compa

View this video to hear more from this interview ▸

If you suspect your patient may have one or a combination of these distinguishing signs and symptoms, consider testing for AADC deficiency.

To learn more about distinguishing signs and symptoms of AADC deficiency and how to test for this condition, visit **AADCInsights.com**.

CT=computed tomography; EEG=electroencephalogram; MRI=magnetic resonance imaging

Accurate identification can help improve the care and management of patients with AADC deficiency[1,2]

Diagnostic pathway for suspected AADC deficiency[2,7]

HYPOTONIA, HYPERTONIA
AND
DELAYED MOTOR DEVELOPMENT
AND
STRUCTURALLY NORMAL MRI

+

MOVEMENT DISORDERS	AND/OR	AUTONOMIC SYMPTOMS
Oculogyric crisis (can be mistaken for seizures)		Ptosis
Dystonia		Excessive sweating
Hypokinesia and/or bradykinesia		Nasal congestion
		Temperature instability

Patients with AADC deficiency may present with one or a combination of symptoms.[2]

TEST FOR AADC DEFICIENCY

Core diagnostic tests	Results
Single gene or genetic panel	Mutation(s) in the *DDC* gene
Plasma enzyme activity assay	**LOW** plasma AADC enzyme activity
AND/OR	
CSF neurotransmitter metabolite panel	**REDUCED** HVA, 5-HIAA, and MHPG **ELEVATED** 3-OMD, L-dopa, and 5-HTP **NORMAL** pterins

Adapted from Himmelreich 2019.[2]

Other tests that may be helpful include[25-28]:

- Blood level measurement of 3-OMD
- Urinary organic acid analysis

Current consensus guidelines recommend performing a CSF neurotransmitter metabolite panel and/or plasma AADC enzyme activity assay in combination with genetic testing to confirm a diagnosis of AADC deficiency.[7]

Visit **AADCInsights.com** to learn more about diagnosing neurotransmitter disorders like AADC deficiency.

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

PTC PINPOINT™

PTC Therapeutics sponsored testing program

Because prompt diagnosis can help improve the care and management of patients with AADC deficiency and other neurotransmitter disorders,[1,2] PTC Therapeutics and Invitae have partnered to offer no-cost genetic testing programs for individuals with a suspected neurotransmitter disorder.

PTC Pinpoint™ Neurotransmitter Disorders Program*
The PTC Pinpoint Program offers testing with the Invitae Neurotransmitter Disorders Panel, which analyzes up to 45 genes that are associated with disorders of monoamine metabolism, GABA metabolism, and neurotransmitter receptors and transporters.

Patients tested through PTC Pinpoint are eligible for post-test genetic counseling to help them and their caregivers understand their test results. This service is made available by Invitae at no charge as part of the program.

Please visit **invitae.com/en/PTC-pinpoint** to learn more about PTC Pinpoint. You can also contact your PTC Therapeutics representative to learn more about this no-charge testing program.

Why test for 3-OMD?

Reduced AADC enzyme activity is the result of an increase in L-dopa, 3-OMD, and 5-HTP, and a decrease in the neurotransmitter metabolites HVA and 5-HIAA.[1,7,8,18]

Typically, the diagnosis of AADC deficiency requires CSF neurotransmitter analysis. However, 3-OMD, which is a catabolic product of L-dopa that accumulates in individuals with AADC deficiency, can be detected in their blood. 3-OMD measurement in plasma represents a less invasive, simple, rapid, and valid measure for detecting AADC deficiency.[26,28]

GABA=gamma-aminobutyric acid.

*If a patient is found to have a pathogenic variant through the PTC Pinpoint program, all of their blood relatives are eligible for family variant testing. These programs are available to eligible patients in the US and Canada.

Identify neurotransmitter disorders like AADC deficiency earlier by looking for distinguishing signs and symptoms

Symptoms of neurotransmitter disorders can overlap with those of other neurological disorders

Accurate identification can help improve the care and management of patients with AADC deficiency[1,2]

One or a combination of red-flag diagnostic clues should prompt testing for a neurotransmitter disorder, like AADC deficiency:

- Oculogyric crises[2,8,23]
- Normal EEG and neuroimaging[2,7,12,13]
- Autonomic symptoms[2]
- Diurnal variation[3,7,24]

PTC Pinpoint™ is a no-charge genetic testing and counseling program for individuals suspected of having a neurotransmitter disorder, such as AADC deficiency

Visit **AADCInsights.com** to learn more about AADC deficiency and how to diagnose this neurotransmitter disorder.

References: 1. Pons R, Ford B, Chiriboga CA, et al. Aromatic L-amino acid decarboxylase deficiency: clinical features, treatment, and prognosis. *Neurology*. 2004;62(7):1058-1065. **2.** Himmelreich N, Montioli R, Bertoldi M, et al. Aromatic amino acid decarboxylase deficiency: molecular and metabolic basis and therapeutic outlook. *Mol Genet Metab*. 2019;127(1):12-22. doi:10.1016/j.ymgme.2019.03.009. **3.** Ng J, Papandreou A, Heales SJ, et al. Monoamine neurotransmitter disorders—clinical advances and future perspectives. *Nat Rev Neurol*. 2015;11(10):567-584. **4.** Hwu PW, Kiening K, Anselm I, et al. Gene therapy in the putamen for curing AADC deficiency and Parkinson's disease. *EMBO Mol Med*. 2021;13(9):e14712. doi:10.15252/emmm.202114712. **5.** Neurotransmitters: What they are, functions & types. Cleveland Clinic. https://my.clevelandclinic.org/health/articles/22513-neurotransmitters#:~:text=Neurotransmitters%20are%20chemical%20messengers%20that,muscle%20cell%20or%20a%20gland. Published March 14, 2022. Accessed June 23, 2022. 6. Ng J, Heales SJR, Kurian MA. Clinical features and pharmacotherapy of childhood monoamine neurotransmitter disorders. *Paediatr Drugs*. 2014;16(4):275-291. doi:10.1007/s40272-014-0079-z. **7.** Wassenberg T, Molero-Luis M, Jeltsch K, et al. Consensus guideline for the diagnosis and treatment of aromatic L-amino acid decarboxylase (AADC) deficiency. *Orphanet J Rare Dis*. 2017;12(1):12. doi:10.1186/s13023-016-0522-z. **8.** Brun L, Ngu LH, Keng WT, et al. Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. *Neurology*. 2010;75(1):64-71. **9.** Manegold C, Hoffmann GF, Degen I, et al. Aromatic L-amino acid decarboxylase deficiency: clinical features, drug therapy and follow-up. *J Inherit Metab Dis*. 2009;32(3):371-380. **10.** Hwu WL, Chien YH, Lee NC, et al. Natural history of aromatic L-amino acid decarboxylase deficiency in Taiwan. *JIMD* Rep. 2018;40:1-6. doi:10.1007/8904_2017_54. **11.** Niemann N, Jankovic J. Juvenile parkinsonism: Differential diagnosis, genetics, and treatment. *Parkinsonism Relat Disord*. 2019;67:74-89. doi:10.1016/j.parkreldis.2019.06.025. 12. Kurian MA, Dale RC. Movement disorders presenting in childhood. *Continuum (Minneap Minn)*. 2016;22(4):1159-1185. **13.** Zouvelou V, Yubero D, Apostolakopoulou L, et al. The genetic etiology in cerebral palsy mimics: the results from a Greek tertiary care center. *Eur J Paediatr Neurol*. 2019;23(3):427-437. doi:10.1016/j.ejpn.2019.02.001. **14.** Krigger KW. Cerebral palsy: an overview. *Am Fam Physician*. 2006;73(1):91-100. **15.** Tasch E, Cendes F, Li LM, Dubeau F, Andermann F, Arnold DL. Neuroimaging evidence of progressive neuronal loss and dysfunction in temporal lobe epilepsy. *Ann Neurol*. 1999;45(5):568-576. doi:10.1002/1531-8249(199905)45:5<568::aidana4>3.0.co;2-p. **16.** Shrimanker I, Tadi P, Sánchez-Manso JC. Parkinsonism. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; May 8, 2022. **17.** Sirven JI. Epilepsy: A Spectrum Disorder. *Cold Spring Harb Perspect Med*. 2015 Sep 1;5(9):a022848. doi:10.1101/cshperspect.a022848. PMID: 26328931; PMCID: PMC4561391. **18.** Hwu WL, Lee NC, Chien YH, et al. AADC deficiency: occurring in humans, modeled in rodents. *Adv Pharmacol*. 2013;68:273-284. **19.** Hwu W-L, Muramatsu S-i, Tseng S-H, et al. Gene therapy for aromatic L-amino acid decarboxylase deficiency. *Sci Transl Med*. 2012;4(134):134ra61. doi:10.1126/ scitranslmed.3003640. **20.** Luo X, Mao Q, Shi J, Wang X, Li CR. Putamen gray matter volumes in neuropsychiatric and neurodegenerative disorders. *World J Psychiatry Ment Health Res*. 2019;3(1):1020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6641567/pdf/nihms-1039924.pdf. Published May 2019. Accessed April 2022. **21.** Ghandili M, Munakomi S. Neuroanatomy, Putamen. StatPearls [Internet]. StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK542170. Updated February 2022. Accessed July 2022. **22.** Lee W-T. Disorders of monoamine metabolism: inherited disorders frequently misdiagnosed as epilepsy. *Epilepsy Seizure*. 2010;3(1):147-153. doi:10.3805/eands.3.147. **23.** Pearson TS, Gilbert L, Opladen T, et al. AADC deficiency from infancy to adulthood: symptoms and developmental outcome in an international cohort of 63 patients. *J Inherit Metab Dis*. 2020;43(5):1121-1130. doi:10.1002/jimd.12247. **24.** Pearson TS, Pons R, Ghaoui R, Sue CM. Genetic mimics of cerebral palsy. *Mov Disord*. 2019;34(5):625-636. doi:10.1002/mds.27655. **25.** Monteleone B, Hyland K. Case report: discovery of 2 gene variants for aromatic L-amino acid decarboxylase deficiency in 2 African American siblings. *BMC Neurol*. 2020;20(1):12. doi:10.1186/s12883-019-1596-8. **26.** Chen P-W, Lee N-C, Chien Y-H, et al. Diagnosis of aromatic L-amino acid decarboxylase deficiency by measuring 3-O-methyldopa concentrations in dried blood spots. *Clin Chim Acta*. 2014;431:19-22. **27.** Chien Y-H, Chen P-W, Lee N-C, et al. 3-O-methyldopa levels in newborns: result of newborn screening for aromatic L-amino-acid decarboxylase deficiency. *Mol Genet Metab*. 2016;118(4):259-263. doi:10.1016/j.ymgme.2016.05.011. **28.** Brennenstuhl H, Kohlmüller D, Gramer G, et al. High throughput newborn screening for aromatic L-amino-acid decarboxylase deficiency by analysis of concentrations of 3-O-methyldopa from dried blood spots. *J Inherit Metab Dis*. 2020;43(3):602-610. doi:10.1002/jimd.12208.

PTC THERAPEUTICS™