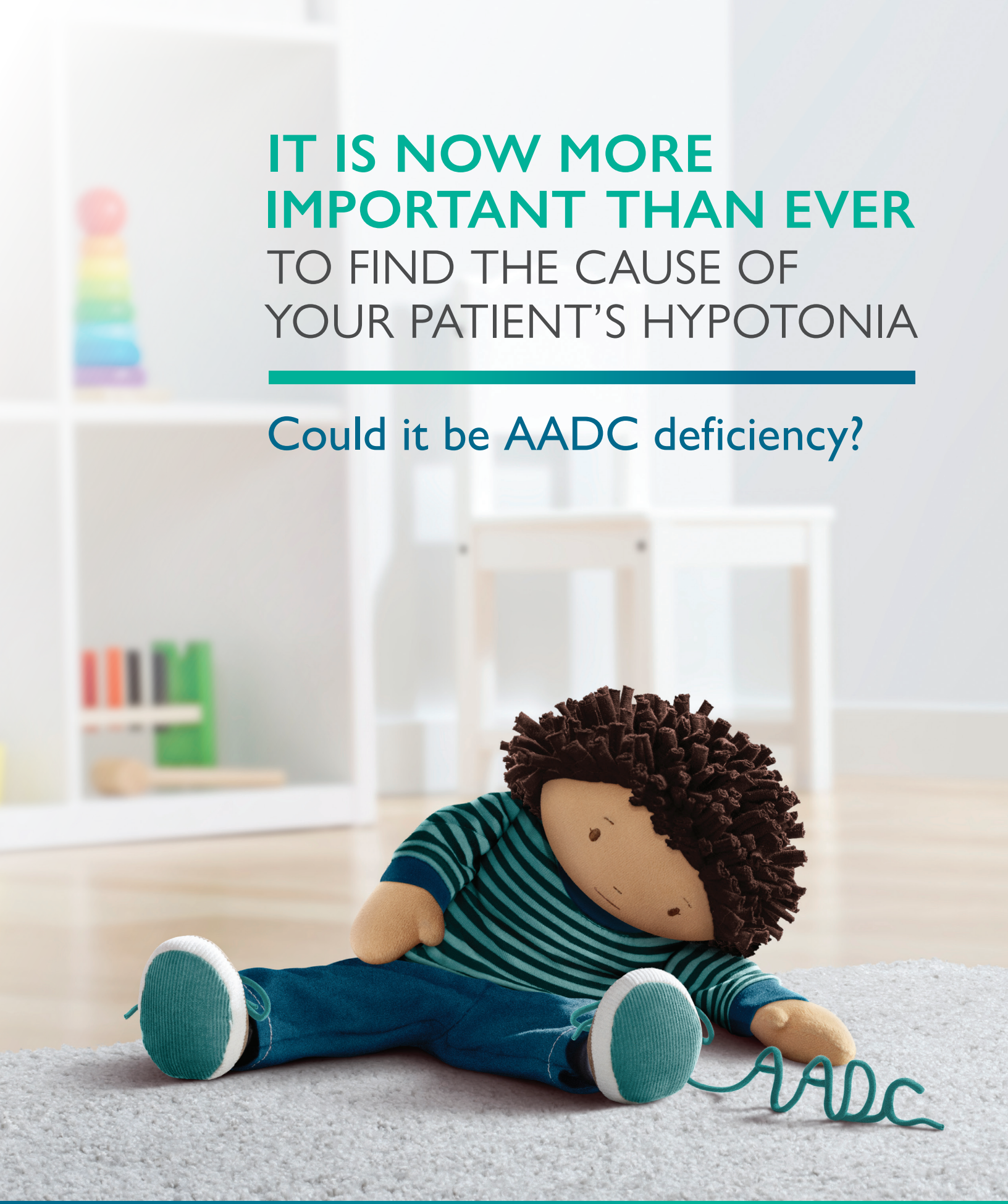
IT IS NOW MORE IMPORTANT THAN EVER TO FIND THE CAUSE OF YOUR PATIENT'S HYPOTONIA

Could it be AADC deficiency?



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

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[1,2]:

- 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 disease are[3-6]:

- 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 such as cerebral palsy and epilepsy, resulting in potential misdiagnosis.[1-4,7-9]

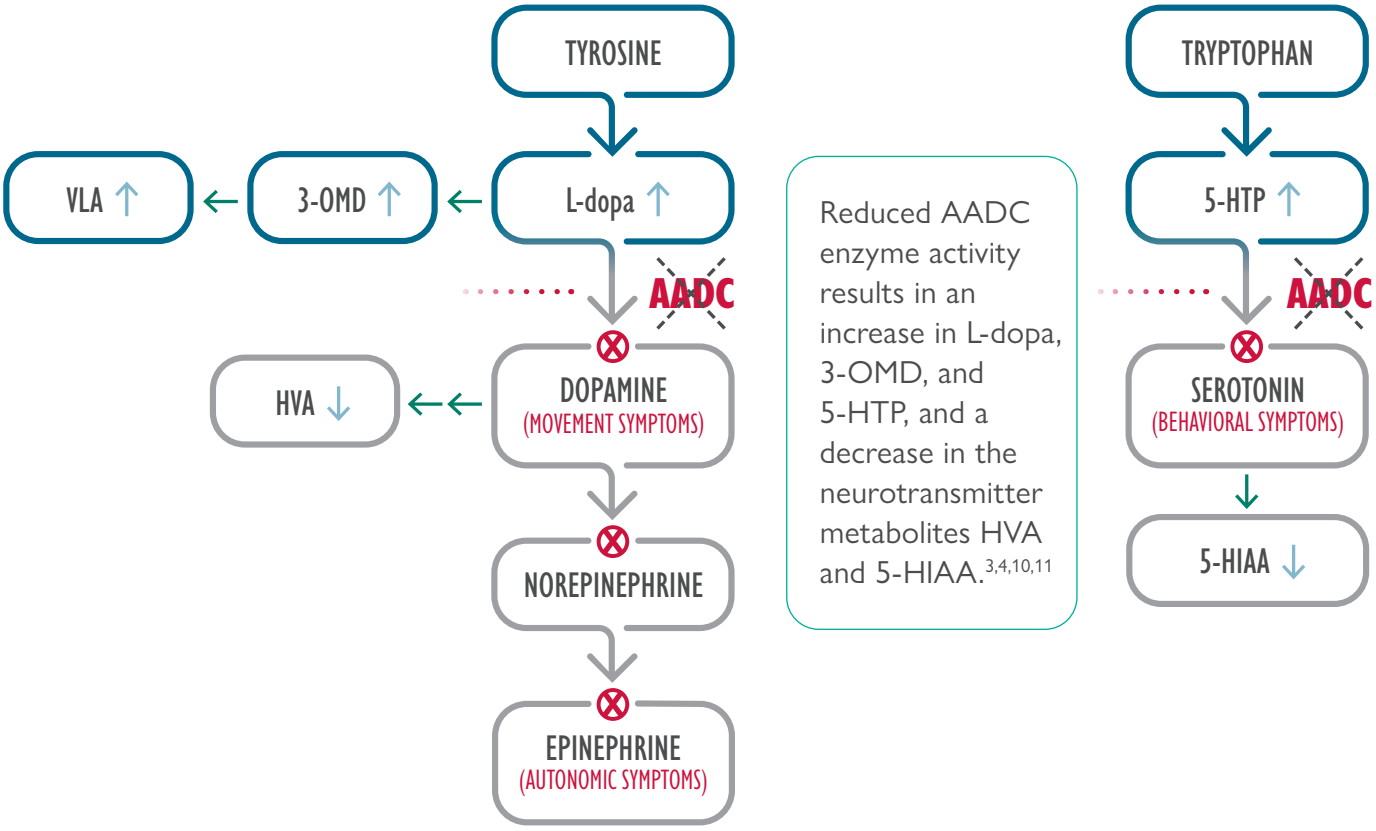
"If all of these symptoms are observed, the diagnosis can be made. But, if you have no experience or knowledge about it, you may have difficulty making a diagnosis."

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

View videos to hear more about symptoms of AADC deficiency

AADC is an enzyme required for biosynthesis of dopamine and serotonin[3]

In 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.[3,4,10,11]



Adapted from Wassenberg 2017.[3]

Accurate identification of disease manifestation can help improve the care and management of patients with AADC deficiency.[10,12]

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

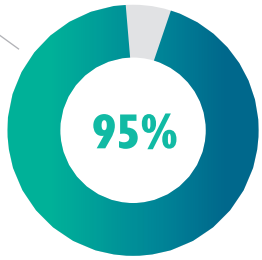
3-OMD=3-O-methyldopa; 5-HIAA=5-hydroxyindoleacetic acid; 5-HTP=5-hydroxytryptophan; HVA=homovanillic acid; L-dopa=L-3,4-dihydroxyphenylalanine; VLA=vanillactic acid.

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[4]:

Hypotonia[4]

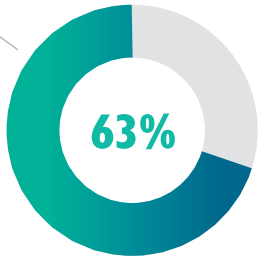
- Most commonly reported symptom



n=74

Developmental delay[4]

- In AADC deficiency, developmental delay may include impairments in head control, crawling, or standing, and speech delays[3,6]

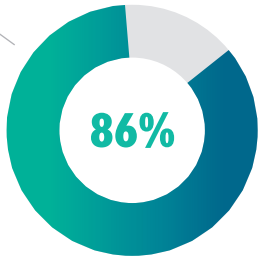


n=49

Movement disorders

Oculogyric crisis[4]

- 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[9]
- Can last a few seconds or persist for several hours, and occur several times per day or week[8]
- May not be present in all cases[4]
- Often misdiagnosed as a seizure, epilepsy, or mitochondrial disease[8,11]



n=67

Others include[4]:

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

Autonomic symptoms include[4]:

- 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[3,4,12]

Despite symptom onset during infancy, diagnosis is typically delayed[3]:

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.[1-4,7-9]

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

POSSIBLE AADC DEFICIENCY MISDIAGNOSES

AADC deficiency symptoms[3,12]	May be diagnosed as[1,7,9,13]
Oculogyric Crisis	Epilepsy
Dystonia • Rigidity • Motor Delay	Cerebral Palsy
Hypotonia • Akinesia • Ptosis	Neuromuscular Disorders

If you have patients with cerebral palsy of unknown etiology or patients with epilepsy that is refractory to treatment, **you may want to consider an alternate diagnosis of a neurotransmitter disorder such as AADC deficiency.**

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[4,12,14]

- 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[8,11]

Normal EEG and neuroimaging[3,7,8,12]

- One study showed that only a small proportion of patients with AADC deficiency had an abnormal EEG, MRI, or CT[4]

Autonomic symptoms[12]

- Multiple signs of autonomic dysfunction[8]

Diurnal variation[1,3,15]

- Motor symptoms become exacerbated or more prominent late in the day and improve with sleep[1,15]

"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 company

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**.

Accurate identification can help improve the care and management of patients with AADC deficiency[10,12]

Diagnostic pathway for suspected AADC deficiency[3,12]

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.[12]

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.[12]

Other tests that may be helpful include[16-19]:

- 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.[3]

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

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,[10,12] PTC Therapeutics and Invitae have partnered to offer no-cost genetic testing programs for individuals with a suspected neurotransmitter disorder or cerebral palsy (CP) spectrum disorder of unknown etiology.

PTC Pinpoint Neurotransmitter Disorders Program

The PTC Pinpoint™ Program offers testing with the Invitae Neurotransmitter Disorders Program, which analyzes up to 27 genes that are associated with disorders of monoamine metabolism, GABA metabolism, and neurotransmitter receptors and transporters.

PTC Pinpoint CP Spectrum Genetic Testing Program

The CP Spectrum Program breaks down many barriers to genetic testing for CP. Through PTC Pinpoint, individuals with symptoms suggestive of CP without evidence for acquired brain injury have access to no-charge genetic testing and counseling. The program analyzes 265 genes and may help to identify an underlying etiology, such as AADC deficiency, which may be amenable to specific medical management or treatment options.

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 provided through GeneMatters™, a third-party genetic counseling service, and is made available by Invitae at no charge as part of the program.

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.

Please visit **www.Invitae.com/PTC-Pinpoint** to learn more about PTC Pinpoint or to order a test. You can also contact your PTC Therapeutics representative to learn more about this no-charge testing program.

GABA=gamma-aminobutyric acid.

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.[3,4,10,11]

Typically, the diagnosis of AADC deficiency requires cerebrospinal fluid (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.[17,19]

Current consensus guidelines recommend performing a CSF neurotransmitter metabolite panel and/or plasma AADC enzyme activity assay, as a less invasive first step in detection, followed by genetic testing to confirm a diagnosis of AADC deficiency.[3]

"3-O-methyldopa is a very reliable marker for AADC deficiency. It accumulates to very high levels in blood and in spinal fluid. So, if you want to screen for AADC deficiency, it's a very good screening biomarker for the disorder."

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

View this video to hear more from this interview ▸

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[10,12]

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

- Oculogyric crises[4,12,14]
- Normal EEG and neuroimaging[3,7,8,12]
- Autonomic symptoms[12]
- Diurnal variation[1,3,15]

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.

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