AROMATIC L-AMINO ACID DECARBOXYLASE (AADC) DEFICIENCY:

A genetic neurotransmitter disease with a devastating clinical course[1-3]

AADC deficiency is a rare, inherited disorder of neurotransmitter synthesis resulting from a mutation in the dopa decarboxylase *(DDC)* gene[1-3]

Patients most often do not achieve developmental milestones and may present with hypotonia, oculogyric crisis, and autonomic symptoms, and require lifelong care[1-4,6]

Mutations in the *DDC* gene result in reduced AADC enzyme activity, leading to severe combined deficiency of the neurotransmitters dopamine, serotonin, noradrenaline, and adrenaline[2-5]

AADC deficiency has the potential to be misdiagnosed due to similarity of symptoms associated with other conditions, including cerebral palsy, epilepsy, and neuromuscular weakness[2,7-10]

The lack of these neurotransmitters leads to movement disorders, autonomic symptoms, and behavioural symptoms[2-4]

Patients with AADC deficiency have been documented worldwide, spanning gender, ethnic origin, and geographic region[2,6]

Consider genetic testing for AADC deficiency in patients with unexplained hypotonia, movement disorders (especially oculogyric crisis), autonomic symptoms, and developmental delay.[2]

PTC THERAPEUTICS

Expert consensus guidelines state that AADC deficiency should be considered in children in whom some or all of the following symptoms go unexplained[2,11]

Symptom presentation in patients with AADC deficiency (%)[3,a]

Hypotonia[2,3,6]

- Most commonly reported symptom

Developmental delay[2,3,6]

- Impairments in head control, sitting, crawling, or standing
- Speech delays

Movement disorders

Oculogyric crisis[2-4,7]

- 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]

- Dystonia (53%)
- Hypokinesia (32%)

Autonomic symptoms[2-4]

- Hyperhidrosis (65%)
- Ptosis (39%)
- Hypersalivation (41%)
- Nasal Congestion (31%)

[a]Percentages based on a clinical study of 78 patients diagnosed with AADC Deficiency.[3]

References: 1. 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. **2.** 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. **3.** 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. **4.** 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. **5.** Hwu WL, Lee NC, Chien YH, et al. AADC deficiency: occurring in humans, modeled in rodents. *Adv Pharmacol.* 2013;68:273-284. **6.** 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. **7.** Lee WT. Disorders of monoamine metabolism: inherited disorders frequently misdiagnosed as epilepsy. *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 19, 2018. **8.** Krigger KW. Cerebral palsy: an overview. *Am Fam Physician.* 2006;73(1):91-100. **9.** Ng J, Papandreou A,Heales SJ, et al. Monoamine neurotransmitter disorders—clinical advances and future perspectives. *Nat Rev Neurol.* 2015;11(10):567-584. **10.** Kurian MA, Dale RC. Movement disorders presenting in childhood. *Continuum (Minneap Minn).* 2016;22(4 Movement Disorders):1159-1185. **11.** Garcia-Cazorla A, Duarte S, Serrano M, et al. Mitochondrial diseases mimicking neurotransmitter defects. *Mitochondrion.* 2008;8(3):273-278.

Diagnostic tests for AADC deficiency[2]

1 Perform[2]

- **a)** Genetic Testing
- **b)** CSF neurotransmitter metabolite panel

AND/OR

- **c)** Plasma enzyme activity assay

2 Interpret[2]

- **a)** Mutation(s) in the *DDC* gene
- **b)** CSF:

  Elevated: 3-OMD, L-dopa and 5-HTP;

  Reduced: 5-HIAA, HVA and MHPG;

  Normal: pterins

AND/OR

- **c)** Plasma: Decreased AADC enzyme activity

3 Other diagnostic tests that may be helpful[2]

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

3-OMD=3-O-methyldopa; 5-HIAA=5-hydroxyindoleacetic acid; 5-HTP=5-hydroxytryptophan; CSF=cerebrospinal fluid; HVA=homovanillic acid; L-dopa=L-3, 4-dihydroxyphenylalanine; MHPG=3-methoxy-4-hydroxyphenylglycol; VLA=vanillactic acid.

For more information about AADC deficiency go to www.AADCInsights.com.au

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ACN: 635 417 711 ABN: 19 635 417 711
Address: Level 11, 500 Collins Street, Melbourne VIC 3000.
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