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Case report

Mild Aromatic L-Amino Acid Decarboxylase Deficiency: As A Reason For Hypoketotic Hypoglycemia In A 4-Year-Old Girl

AADC deficiency: As a Reason for Hypoketotic Hypoglycemia

Merve Yoldas Celik[1], Ebru Canda[1], Havva Yazici[1],Fehime Erdem[1], Ayse Yuksel Yanbolu[1], Ayca Aykut[2], Asude Durmaz[2], Ahmet Anik[3], Sema Kalkan Ucar[1], Mahmut Coker[1]

[1]Department of Pediatrics, Division of Pediatric Metabolism and Nutrition, Ege University Faculty of Medicine, Izmir, Turkiye

[2]Department of Genetics, Ege University Faculty of Medicine, Izmir, Turkiye

[3]Department of Pediatrics, Division of Pediatric Endocrinology, Adnan Menderes University, Aydin, Turkiye

What is already known on this topic?

- AADC deficiency is an inherited metabolic disease that leads to a deficiency of serotonin, dopamine, epinephrine, and norepinephrine.
- Neurological findings are dominant due to deficiencies in neurotransmitter synthesis, but hypoglycemia can occur by autonomic dysfunction.

What this study adds?

- The first finding of our case with mild AADC deficiency was hypoglycemia.
- In patients presenting with hypoglycemia, AADC deficiency should be considered in the differential diagnosis, even if there are no neurological findings.

Abstract

Aromatic L-amino acid decarboxylase (AADC) deficiency is a disease in which neurological findings are dominant due to deficiencies in neurotransmitter synthesis; hypoglycemia caused by autonomic dysfunction is one of the symptoms that may be encountered. Here we report a mild AADC deficiency presenting with hypoglycemia without a neurological sign. A 4-year-old girl presented with recurrent hypoglycemia. Her growth and development were normal. Plasma insulin and cortisol values were normal in the sample at the time of hypoglycemia. The C8:1-Carnitine elevation was detected in the acylcarnitine profile. The clinic exome panel was performed with the suggestion of a fatty acid oxidation defect. However, a homozygous variant in the *DDC* gene was detected. On top of that, CSF neurotransmitter analysis revealed low 5-hydroxy indol acetic (5 HIAA) and homovanillic acid (HVA) and high 3-O-methyl-dopa and methyltetrahydrofolate (5 MTHF) consistent with AADC deficiency. Plasma AADC enzyme activity was low. The episodes of hypoglycemia were treated with uncooked cornstarch. Our case emphasizes that AADC deficiency should be considered in patients with hypoglycemia.

Keywords: Aromatic L-amino acid decarboxylase deficiency, AADC deficiency, hypoglycemia, neurotransmitter deficiency

Merve Yoldas Celik, MD , Department of Pediatric Metabolism, Faculty of Medicine, Ege University, Izmir 35040, Turkiye
+905055904856
drmerveyoldas@yahoo.com
0000-0003-0015-9807
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Introduction

Hypoglycemia is one of the common biochemical findings in endocrine and inherited metabolic disorders. Commonly known specific metabolic disorders causing hypoglycemia include glycogen storage diseases, gluconeogenesis disorders, fatty acid oxidation defects, and ketolysis defects. (1) Identifying and treating the cause of hypoglycemia is of great importance. Therefore, the ultra-rare metabolic causes of hypoglycemia, such as neurotransmitter disorders and particular Aromatic L-amino acid decarboxylase (AADC) deficiency, should be kept in mind. (2)

AADC is an essential enzyme in synthesizing monoamine neurotransmitters serotonin and dopamine. Dopamine is the precursor of epinephrine and norepinephrine (*figure 1*). AADC deficiency is an autosomal recessive inherited metabolic disease that causes a deficiency of serotonin, dopamine, epinephrine, and norepinephrine. AADC deficiency manifests with neurologic symptoms such as developmental delay, dystonia, oculogyric crisis, hypotonia, and autonomic findings in the early stages of life. The phenotypic spectrum of the disease is broad. Based on the clinical description, it was classified as mild, moderate, and severe according to the severity of neurological symptoms. The mild phenotype may present autonomic symptoms without significant movement disorders(3).

AADC deficiency leads to redeuced dopamine, norepinephrine, and epinephrine levels. Catecholamines have essential counter-regulating functions for hypoglycemia, such as stimulaton of gluconeogenesis and lipolysis (*figure 1*). Hypoglycemia may not be expected as the primary finding in AADC deficiency, where the critical finding is neurological symptoms. In addition to neurological findings, hypoglycemia in intercurrent diseases has been reported in a small number of cases (4-13). Hypoglycemia is thought to develop from the deficiency of catecholamines, which are contra-insulin hormones. This report presents a case of AADC deficiency diagnosed with hypoglycemia without neurological findings.

Case Report:

A 4-year-old girl was presented with four recurrent hypoglycemic attacks. The patient was born at 38 weeks, with c-section delivery at 2700 grams. Prenatal history was unremarkable. Due to meconium staining, she was hospitalized for two days in the neonatal intensive care unit. She experienced jaundice in the neonatal period but did not need phototherapy. She has got breast milk for 18 months. Her developmental stages were expected, in line with her age (sat unsupported at seven months, speech at 12 months, walked unsupported at 18 months). There was a history of third-degree cousin marriage between the parents.

On physical examination, body weight was -1.4 SDS, height was -1.79 SDS, and head circumference was -0.43 SDS. There was no dysmorphic finding, no organomegaly, and a detailed neurological examination was normal. She had normal muscle bulk, tone, and power. Deep tendon reflexes were normal. She had no movement disorder findings like hypokinesia, dystonia, or oculogyric crises. The patient had a history of hypoglycemia accompanied by a seizure after diarrhea for the first time at the age of 3.5 years. She experienced hypoglycemia four times in total. Hypoglycemia was usually observed after about 10 hours of fasting and diarrhea. The fasting test for the etiology of hypoglycemia was performed with metabolic and endocrinological sampling at 35 mg/dL glucose level at the 12th hour of the fasting. Insulin, adrenocorticotropic hormone (ACTH), and cortisol levels were normal. The urine ketone was negative, and the lactate level was in a normal range. The patient was unresponsive to glucagon administration. After intravenous glucose infusion at the time of hypoglycemia, blood glucose was recorded as 230 mg/dl. In the sample taken at the time of hypoglycemia, there was a C8:1 carnitine (1.0 µmol/L, N:<0.47) elevation in the acylcarnitine profile; tiglylglycine excretion in urine organic acid and plasma amino acid profiles were average. Complete blood count with differential, liver, and kidney function tests, lipid profile, ammonia, and lactate levels were expected in the laboratory analysis. Eye examination and hearing test were regular. Abdominal ultrasonography and echocardiography were normal. Cranial MRI and electromyography were normal.

Hypoketotic hypoglycemia, high levels of C8:1, and low insulin levels were compatible with fatty acid oxidation defects. However, the clinical exome sequencing panel revealed a homozygous p.Asp15Gly variant in the *DDC* gene. This variant was classified as variant of uncertain significance [VUS (PM2-PP3)], according to the American College of Medical Genetics (ACMG) criteria. Upon this result, a lumbar puncture was performed, and low cerebrospinal fluid (CSF) levels of 5-Hydroxyindole-3-acetic acid (5-HIAA) and homovanillic acid (HVA) and high levels of 3-O-methyl-dopa and 5-methyltetrahydrofolate (5-MTHF) was identified consistent with AADC deficiency. AADC activity was low. The laboratory values of the patient are presented in Table 1. The patient was diagnosed with AADC deficiency, confirmed by enzymatic and genetic analysis. 100 mg/day of pyridoxine treatment was started. The episodes of hypoglycemia were treated with raw cornstarch (1 g/kg).

Discussion

In this report, we emphasized that the initial finding of a case diagnosed with mild AADC deficiency was hypoglycemia. AADC deficiency is an ultra-rare inherited metabolic disease defined by the reduced activity of AADC, the key enzyme of neurotransmitters (dopamine and serotonin) synthesis. Just about 150 patients have been reported before. Children with this condition are usually diagnosed in their first year of life. The cardinal sign of AADC deficiency is neurological symptoms, mainly hypotonia and oculogyric crises. In addition, autonomic nervous system dysfunction may cause extra neurological findings like gastrointestinal problems (diarrhea, constipation), feeding difficulties, nasal congestion, unstable body temperature, low blood pressure, and hypoglycemia (3).

Although hypoglycemia is not a cardinal finding of this disease, it was reported in 5 of the total 82 patients in Pediatric Neurotransmitter Diseases at BioPKU.org database. Hypoglycemia has been associated with epinephrine deficiency in AADC deficiency (10, 14). According to the literature, episodes of hypoglycemia are not constant in patients with AADC deficiency and were documented only in patients with a severe phenotype (7, 13). We summarized clinical and laboratory data of all AADC deficiency patients with hypoglycemia in Table 2. Remarkably, our patient had hypoglycemia episodes as the primary symptom, and no neurological signs were observed except for a seizure triggered by hypoglycemia. Arnoux et al. reported a similar patient with mild AADC deficiency, a 5-year-old girl with episodes of hypoglycemia and diarrhea who had only hypomimia and dyspraxia as neurological findings (5). Consequently, according to our knowledge, only two patients presented with hypoglycemia and were diagnosed with mild AADC deficiency based on the differential diagnosis of hypoglycemia. Routine first-line metabolic investigations for hypoglycemia may not indicate AADC deficiency. Lactate, ammonia, acylcarnitine profile, and plasma amino acid analysis are normal in these patients. However, patients with AADC deficiency may be identified by elevated vanil lactic acid in urine organic acid analysis due to degradation of 3-O-methyl-1-dopa(3-OMD) to vanil lactic acid (7). In our patient, tiglylglycine excretion was recorded due to fasting in the urine organic acid analysis, and there was no vanil lactic acid excretion. A low ketone level at the time of hypoglycemia may suggest a diagnosis of hyperinsulinism or fatty acid oxidation deficiency. However, NE and E levels decrease in AADC deficiency, leading to an impaired glucagon response to hypoglycemia, which explains the low ketone levels. In particular, the main laboratory test to reach the AADC deficiency diagnosis is the measurement of neurotransmitter levels. While the pterin level is standard in the CSF analysis, there are high 3-O-methyl-1-dopa and 5-HTP and decreased HVA and 5-HIAA values. 3-OMD is a disease-specific metabolite, and showing its elevation in plasma or dry blood may be hope for early detection of patients with a newborn screening program in the future (15). Demonstrating AADC enzyme deficiency in plasma supported the molecular diagnosis. The present case report emphasized that AADC deficiency should be considered in the differential diagnosis of patients presenting with hypoglycemia, even in the absence of classical neurological findings of the disease.

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Figures:

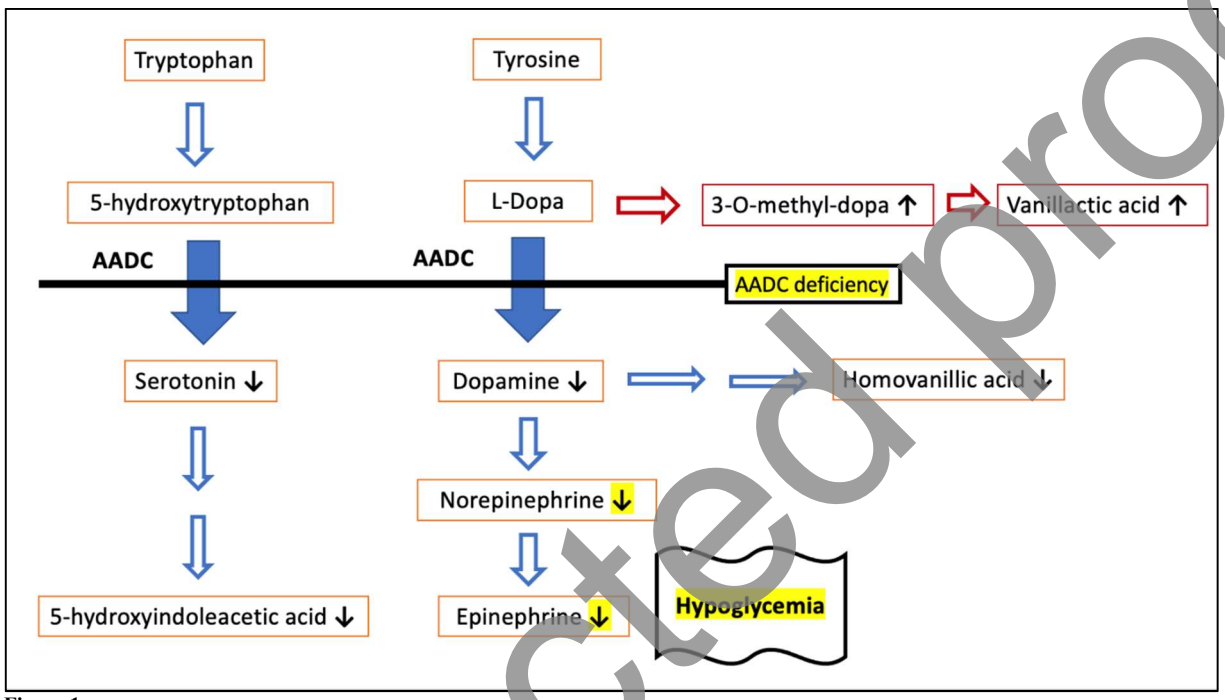

Figure 1:
Norepinephrine (NE) and epinephrine (E) maintain glycemia levels by stimulating glucagon release, glycogenolysis, and food consumption and inhibiting insulin release. Studies on Marie LS et al. found that the absence of catecholamines in dopamine β-hydroxylase-null mice resulted in chronically low blood glucose levels, impaired glucagon response to hypoglycemia, and elevated insulin levels, suggesting that NE and E are necessary for glucose homeostasis.(14) Isolated deficiency in a counter-regulatory hormone (e.g.,hGH or cortisol) is sufficient to expose the patient to hypoglycemia. Consequently, hypoglycemia in AADC deficiency is probably only the consequence of the altered synthesis of dopamine-derived catecholamines.

Table 1: Laboratory characteristics of the patient

	Patient	Normal range
Blood (Plasma /Serum)		
Glucose, mg/dL	35	>55
Insulin (during hypoglycemia), µU/mL	0.4	<1
C-peptide (during hypoglycemia), ng/mL	0.07	<0.30
Cortisol (during hypoglycemia), µg/dL	30.9	>20
GH (during hypoglycemia), ng/mL	15.2	
Prolactin, µg/L	25	4.70-23.3
Plasma activity of AADC, pmol/min/mL	4	33-79
CSF		
CSF homovanillic acid (HVA), nmol/L	144.9	233-928
CSF 5-hydroxyindolacetic(5-HIAA), nmol/L	39	74-345
CSF 3-O-methyl-dopa, nmol/L	415.2	<150
CSF 5-hydroxytryptophan (5-HTP), nmol/L	34.2	<10
Urine organic acid analysis		
Tiglylglycine mmol/mol creatinine	4	N.D.
Vanil lactic acid	N.D.	N.D.

Abbreviations: AADC, Aromatic L-Amino Acid Decarboxylase; CSF, cerebrospinal fluid; GH, growth hormone; N.D, not detectable; IGF-I, Insulin-like growth factor-I.

Table 2: AADC deficiency patients with hypoglycemia in the published literature.

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**	**Patient 8**	**Patient 9**	**Patient 10**	**Patient 11**	**Patient 12**	**Patient 13**
Reference	Present study	(Arnoux et al., 2013)	(Pons et al., 2004)	(Dai et al., 2020)	(Dai et al., 2020)	(Abdenur et al., 2006)	(Christoph Korenke et al., 1997)	(Spitz et al., 2017)	(Helman et al., 2014)	(Helman et al., 2014)	(Lee et al., 2009)	(Manegold et al., 2009)	(Manegold et al., 2009)
Gender	Female	Female	Male	Male	Male	Male	Female	Female	Male	Female	Female	Male	Female
Age at onset	42 months	3 years	2 months	3 months	3 months	2 days	3 months	3 months	7 years	10 months	3 months	4 months	5 years
Disease phenotype	Mild	Mild	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe
Hypoglycemia	+	+	+	+	+	+	+	+	+	+	+	+	+
Diarrhea	+	+	+	-	-	-	-	+	-	-	-	-	-
Temperature instability	-	-	-	-	+	+	+	**N/A**	-	-	-	-	+
Hyperhidrosis	-	-	+	+	+	+	+	+	+	-	+	+	-
Nasal congestion	-	+	+	+	+	-	-	+	+	-	+	-	-
Feeding problems	-	-	+	+	-	+	+	**N/A**	+	+	+	+	+
Failure to thrive	-	-	+	+	+	+	+	**N/A**	**N/A**	**N/A**	+	**N/A**	**N/A**
Movement disorders	-	+	+	+	+	+	+	+	+	+	+	+	+
Oculogyric crisis	-	-	+	+	+	+	+	+	+	+	+	+	+
Irritability	-	-	+	+	-	+	+	+	+	-	+	+	+
Developmental delay	-	-	+	+	+	+	+	+	+	+	+	+	+
Epileptic seizures	+	+	-	-	-	-	-	-	+	-	-	-	-
Sleep problems	-	-	+	+	+	-	-	+	**N/A**	**N/A**	-	+	-
Hyperprolactinemia	+	+	N/A	+	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Urine organic acids	tiglylglicine	N/A	N/A	Normal	Normal	vanillactic acid	vanillactic acid	vanillactic acid	N/A	N/A	N/A	N/A	N/A
AADC activity, pmol/min/ml	4	5	<1	N/A	N/A	<1	2.6	5	2.6	1.5	3.9	0.2	1.6

(N 33-79)													
AADC gene mutations; Variant 1	c.44A >G	c.97G >T	c.1222 C>A	c.714+ 4A>T	c.714+ 4A>T	N/A	N/A	c.823 G>A	c.665T >C	N/A	c.714+ 4A>T	N/A	c.206 C>T
AADC gene mutations; Variant 2	c.44A >G	c.1385 G>C	C102T (prem ature stop codon)	c.106 G>A	c.714+ 4A>T	N/A	N/A	c.823 G>A	c.665T >C	N/A	c.1234 C>T	N/A	c.439 A>C