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CASE REPORT

Widening Phenotypic Spectrum of AADC Deficiency, a Disorder of Dopamine and Serotonin Synthesis

Guy Helman · Maria Belen Pappa · Phillip L. Pearl

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Abstract *Objectives*: Aromatic amino acid decarboxylase deficiency presents with prominent extrapyramidal and autonomic features and CSF monoamine deficiency with increased 3-*O*-methyldopa, a by-product of accumulated L-DOPA. Less than 100 cases have been identified. The disease is typically associated with a severe phenotype and worse prognosis in females. Gene transfer technology has been implemented using an adeno-associated virus encoding AADC in the putamen bilaterally.

Methods: We describe the phenotype/genotype in a cohort of five cases showing a heterogeneous phenotype and variably intact response to pharmacologic therapy.

Results: Five patients (age range 2–10 years, mean 5 years, 3M/2F) with confirmed AADC deficiency are described. Four (3M/1F) have had improvement on combinations of dopaminergic agonists, MAO inhibitors, pyridoxine/P5P, and folinic acid. Each presented with hypotonia, decreased voluntary movement, dystonia, irritability, and oculogyric crises. Two (1M/1F) are independently ambulatory and are not dependent on gastrostomy tube feedings; the 9-year-old girl is reading single words. One female has a severe phenotype including recurrent hypoglycemic events associated with bradycardia, although the latter have resolved with chronic anticholinergic therapy. One Taiwanese boy had the common homozygous mutation, and otherwise we describe five new DDC mutations.

Conclusions: We report a wider phenotypic spectrum including intact response to pharmacologic management and milder outcome in a female, as well as five new mutations. Four of five patients have improved on combination therapy including a dopamine agonist, MAO inhibitor, pyridoxal-5′-phosphate, and folinic acid. The advent of viral-mediated gene therapy in AADC deficiency renders expanded knowledge of the outcome increasingly important.

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G. Helman · M.B. Pappa
Department of Neurology, Children's National Medical Center, Washington, DC, USA

P.L. Pearl (✉)
Division of Epilepsy and Clinical Neurophysiology, Boston Children's Hospital, Boston, MA 02115, USA
e-mail: Phillip.Pearl@childrens.harvard.edu

Introduction

Aromatic L-amino acid decarboxylase (AADC) deficiency (MIM 608643) is a neurotransmitter metabolism disorder inherited in an autosomal recessive fashion. AADC is a pyridoxal-5′-phosphate-dependent enzyme that functions in the catecholamine biosynthetic pathway (Pons et al. 2004; Hyland 2007). It is responsible for synthesizing dopamine and serotonin through decarboxylation of L-DOPA and 5-hydroxytryptophan. Mutations in *DDC* (MIM 107930) (Hyland 2007; Brun et al. 2010) lead to deficiency of serotonin and dopamine and their downstream metabolites, all components of the monoaminergic system (Lee et al. 2009; Hwu et al. 2012; Shih et al. 2013).

AADC deficiency is a rare condition that usually presents in infancy or early childhood. The most common symptoms are developmental delay, oculogyric crises, and dystonia (Hyland 2007; Brun et al. 2010). CSF studies are pathognomonic, showing reduced homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations, with increased L-DOPA and 3-*O*-methyldopa (Haliloğlu et al. 2012). Pyridoxal-5′-phosphate is a cofactor for

AADC, and a similar CSF profile can be seen in pyridoxal-5′-phosphate dependency (Mills et al. 2005). The diagnosis is confirmed through *DDC* gene sequencing or quantification of plasma AADC enzymatic activity.

Treatment strategy is based on a regimen compensating for lack of AADC activity through monoamine oxidase (MAO) inhibitors, dopaminergic agonists, and pyridoxine or the active form pyridoxal-5′-phosphate (PLP) (Allen et al. 2009; Brun et al. 2010). Folinic acid supplementation was added due to the possibility of cerebral folate depletion as a result of methylation of accumulated L-DOPA (Brun et al. 2010). Little to no improvement with therapy has been described (Swoboda et al. 2003) or even deterioration following initial response to therapy (Chang et al. 2004). It has been suggested that males respond to treatments better than females, based on a study that grouped responses to treatment into two groups: one who responded well to treatment (mostly males) and another who did not respond well to treatment (mostly females with one male) (Pons et al. 2004). The second group often developed treatment-related dyskinesias, and it was suggested that females are more dependent on dopamine levels (Pons et al. 2004). Transdermal rotigotine was efficacious in the early stages of AADC of an affected male; however, the treatment was not effective in his older, more impaired brother (Mastrangelo et al. 2013).

Recently, gene therapy has been used in cases of AADC deficiency (Hwu et al. 2012; Zwagerman and Richardson 2012; Chtarto et al. 2013; Lee et al. 2013). Gene transduction through adeno-associated virus (AAV) was used in a group of patients presented by Hwu et al. (Hwu et al. 2012). AAV2 vector-mediated delivery of the human *DDC* gene (AAV2-hAADC) into the putamen was used to promote motor activity, as the putamen is the major site of AADC activity in the brain. All four patients had gains in body weight and motor function, in addition to reduced oculogyric crises, 1 year after gene transfer (Hwu et al. 2012).

While Brun et al. (2010) presented a summary of 78 AADC patients published to date, less than 100 cases have been reported in the literature (Brun et al. 2010). In light of novel gene therapies for AADC deficiency, we present clinical details on a cohort of five patients with broad clinical variability, four novel mutations in *DDC*, and different responses to treatment.

Case Reports

Patient 1 is a 4-year-old boy with hypotonia noted at birth, gastroesophageal reflux at 2 months, and onset of prolonged oculogyric crises at 3 months. At 7 months of age, distal dystonic movements of the extremities were observed during episodes of upward gaze. Other manifestations were decreased head control, feeding dysfunction, hypersalivation, athetosis, hypokinesis, ptosis, excessive diaphoresis, and irritability.

CSF neurotransmitter profile showed decreased concentrations of HVA (88, normal range 294–1,115) and 5-HIAA (9, normal range 129–520), with elevated 3-*O*-methyldopa (754, normal range <300) and normal biopterin and neopterin levels. The plasma AADC activity level was undetectable. *DDC* sequencing showed compound heterozygosity with mutations at exon 3 (c.289delGfs +20X), leading to formation of a premature stop codon, and exon 6 (c.629C>T p.P210L). Upon diagnosis, the patient was treated with a combination of pramipexole, pyridoxal-5′-phosphate, folinic acid, and tranylcypromine with marked improvement in oculogyric crises and progressive mobility. The patient is now walking independently and has voluntary hand use, marking a dramatic improvement in functionality. Persistent symptoms at age four include moderate hypotonia, increased drooling, feeding difficulties (although feeds completely orally), and nonverbal status.

Patient 2 is a 10-year-old boy that first came to medical attention due to decreased head control and clenched hands shortly before his first birthday. He rolled over at 18 months and by 2 years had a vocabulary of about 40 words, but subsequently lost these skills. His initial diagnosis was cerebral palsy of unknown etiology. The patient had several hospitalizations for dehydration and hypoglycemia, once with a hypoglycemic seizure without recurrence. Other manifestations were ptosis, oculogyric crises, facial hypokinesia, diaphoresis, poor feeding, nasal stuffiness, and hypersalivation.

The diagnosis was established following a CSF monoamine profile of low HVA and 5-HIAA levels and plasma AADC enzymatic activity of 2.6 pmol/mL/min (normal range 36–129). *DDC* sequencing resulted in a novel homozygous missense mutation of exon 6 (c.665 T>C, p.L222P). On exam at 10 years, he is stable on combined therapy of pramipexole, pyridoxal-5′-phosphate, folinic acid, and tranylcypromine. Oculogyric crises have resolved. Dystonic movements, excessive drooling, and nasal stuffiness have improved. Significant bilateral ptosis persists, but the patient is able to take steps with support. Cognitive progress has been noted with intact reception for multistep commands although without expressive verbal language.

Patient 3 is a 4-year-old girl with unusual ocular movements observed in the first weeks of life. These evolved into oculogyric crises and episodic torticollis, associated with staring and orobuccal dyskinesias including lip smacking, by 2 months of age. She developed choreoathetosis and episodic unresponsiveness associated

with oxygen desaturation. Dysautonomic signs included unexplained swings in heart rate from low 50s to 180 beats per minute, and she did not appear to perceive pain. She had multiple hospitalizations the first 3 years of life due to intermittent hypoglycemia and bradycardia.

The patient was diagnosed with AADC deficiency following ascertainment of CSF HVA of 94 nM (normal range 294–1,115), 5-HIAA < 5 nM (129–520), 3-*O*-methyldopa elevated at 630 nM (<300), and AADC enzymatic activity level of 1.5 pmol/mL/min (36–129). Her examination at 14 months of age showed minimal voluntary movement and awareness other than apparent ability to recognize familiar voices. She has persistent hypotonia, ptosis, and dyskinesias and is gastrostomy tube dependent. Her episodic bradycardia stopped with chronic anticholinergic activity utilizing oral hyoscyamine and scopolamine patches. Her therapy otherwise includes ropinirole, leucovorin, and pyridoxal-5′-phosphate, but there has been minimal developmental progress.

Patient 4 is a 2-year-old male of Taiwanese descent who presented at 4 months of age due to developmental delay, decreased head control, and impaired visual tracking. At 7 months, he manifested generalized hypotonia, paroxysmal dystonia, and oculogyric crises. Diagnosis was established by undetectable levels of HVA and 5-HIAA on CSF neurotransmitters and elevated 3-*O*-methyldopa of 453 nM (<300). Plasma AADC enzymatic activity level was 0.53 pmol/mL/min ($N > 8$). The patient was homozygous for the IVS 6+4, A>T mutation.

The patient was first seen on ropinirole and pyridoxine therapy. Severe failure to thrive was treated after the first birthday with gastrostomy tube placement, and the medication program was transitioned to pramipexole, pyridoxal-5′-phosphate, and folinic acid. Within 4 months, the patient demonstrated improvement in motor tone, communication, and emotional stability. Persistent deficits at 2 years of age are poor head control, bilateral ptosis, less frequent and sustained but intermittent oculogyric crises, lower extremity dystonia, and nonambulatory status.

Patient 5 is a 9-year-old female who presented at 4 months of age with hypotonia and failure to gain motor milestones. Her diagnosis was established at age 7½ years following lumbar puncture indicated because of the presence of ataxia and proximal muscle weakness and a diagnostic label of cerebral palsy but without an identified etiology. Lumbar puncture showed CSF HVA of 72 (218–852), 5-HIAA 22 (66–33), and 3-*O*-methyldopa of 729 (<100). The AADC activity level in plasma was <1.5 (36–129), and the *DDC* gene sequencing showed compound heterozygosity with mutations at exon 3 (c.260C>T p.P87L) and exon 5 (c.446G>A p.S149T).

Exam at 9 years of age shows significant progress on combined treatment of bromocriptine and pyridoxine. She has no feeding dysfunction, improved ability to focus, intact reading ability of simple words, some speech (however, most interactions manifest by crying or tearing), and independent walking, albeit it for short distances. Persistent signs and symptoms are nasal stuffiness, mild ptosis, irritability, choreoathetosis, and hypersalivation. She has some unusual eye movements of upward gaze which are not sustained oculogyric crises.

Discussion

We present a cohort of five patients with AADC deficiency with a demonstration of broad phenotypic expression (Table 1). Of these, four (three males and one female) are doing relatively well and responding to therapy utilizing combinations of a dopaminergic agonist, MAO inhibitor, pyridoxine or P5P, and folinic acid. The prospect of gene therapy in AADC deficiency renders expanded knowledge of the phenotypic spectrum and natural history of the disorder increasingly important (Hwu et al. 2012). The Jake database reports 83 cases of AADC deficiency worldwide (JAKE database available at http://www.biopku.org/bioPKU_databasesJAKE.asp, accessed January 28, 2014). We contribute another five and report five new mutations in the *DDC* gene.

All five of our patients presented with characteristic features including hypotonia, decreased motor development and voluntary movement, dystonia, irritability, and oculogyric crises. Three of our patients, two males and one female, have intact gait and are not dependent on gastrostomy tube feedings. One female has a severe phenotype including recurrent hypoglycemic events associated with bradycardia, although the latter have resolved with chronic anticholinergic therapy. Hypoglycemia was an intermittent problem in two of our patients and has been described in the syndrome, attributed to a defect in synthesis of dopamine and hence catecholamines (Arnoux et al. 2013). One male of Taiwanese descent affected with the common IVS6+4 A>T mutation, reported in over 80% of Taiwanese patient populations (Lee et al. 2013; Shih et al. 2013), has a severe phenotype but has responded to combination medication therapy along with gastrostomy tube feedings. One 9-year-old girl on a combined regimen is now walking, verbalizing, and making developmental gains, which is relatively promising in light of prior reports reporting a worse prognosis in females (Tay et al. 2013).

Three of our five patients have improved on a combined therapy typically including a dopamine agonist, MAO inhibitor, and pyridoxal-5′-phosphate. AADC deficiency is characterized by decreased biogenic amines and their downstream metabolites and accumulation of 3-*O*-methyldopa as

Table 1 Clinical overview of AADC patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Current age (years)	4	10	4	2	9
Sex	Male	Male	Female	Male	Female
Age at diagnosis	16 months	7 years	10 months	13 months	7.5 years
Diagnostic confirmation	DDC sequencing: Exon 3: c.289delGfs +20X (Het)[a] Exon 6: c.629 C>T, p.P210L (Het)[a] AADC enzyme activity: <1.5 pmol/ mL/min	DDC sequencing: Exon 6: c.665T>C, p.L222P[a] (homozygous) AADC enzyme activity: 2.6 pmol/mL/min	AADC enzyme activity: 1.5 pmol/mL/min	DDC sequencing: IVS6+4 A>T (homozygous) AADC enzyme activity:0.53 pmol/ mL/min	DDC sequencing: Exon 3 c.260C>T, p.P87L (Het)[a]; Exon 5 c.446G>A, p.S149T (Het)[a] AADC enzyme activity:<1.5 pmol/ mL/min
Outcome	Ambulatory; feeds independently; nonverbal	Stands; takes steps with support; G-tube dependent; nonverbal	Severe; G-tube dependent; nonambulatory; nonverbal	Severe; G-tube dependent; nonambulatory; nonverbal	Ambulatory; feeds independently; verbal

[a] Newly reported *DDC* mutations

a by-product of accumulated L-DOPA. While the disorder has traditionally been associated with a severe presentation and poor responsiveness to medical intervention (Alfadhel and Kattan 2014), additional reports such as ours demonstrate a wider phenotypic spectrum. This must be a consideration in the selection of patients for future novel therapies including viral-mediated gene therapy.

Synopsis

Aromatic amino acid decarboxylase deficiency is a rare disorder with a heterogeneous phenotypic spectrum that must be taken into account in evaluating prospective gene transfer technologies.

Compliance with Ethics Guidelines

The authors, Guy Helman, Maria Belen Pappa, and Phillip Pearl, report no conflicts of interest. All patients were evaluated in good clinical practice. IRB approval was obtained (BCH protocol 3660). Guy Helman was responsible for data review and manuscript preparation and submission. Maria Belen Pappa provided data and manuscript review. Phillip Pearl was responsible for data collection and analysis, manuscript oversight, and ethical conduct oversight.

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