Libertas Academica
FREEDOM TO RESEARCH

Open Access: Full open access to this and thousands of other papers at http://www.la-press.com.

Journal of Central Nervous System Disease

Aromatic Amino Acid Decarboxylase Deficiency Not Responding to Pyridoxine and Bromocriptine Therapy: Case Report and Review of Response to Treatment

Majid Alfadhel[1] and Rana Kattan[2]

[1]Division of Genetics, Department of Pediatrics, King Saud bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Riyadh, Saudi Arabia. [2]Division of General Pediatrics, Department of Pediatrics, King Saud bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Riyadh, Saudi Arabia.

ABSTRACT: Aromatic L-amino acid decarboxylase (AADC) deficiency (MIM #608643) is an autosomal recessive inborn error of monoamines. It is caused by a mutation in the *DDC* gene that leads to a deficiency in the AADC enzyme. The clinical features of this condition include a combination of dopamine, noradrenaline, and serotonin deficiencies, and a patient may present with hypotonia, oculogyric crises, sweating, hypersalivation, autonomic dysfunction, and progressive encephalopathy with severe developmental delay. We report the case of an 8-month-old boy who presented with the abovementioned symptoms and who was diagnosed with AADC deficiency based on clinical, biochemical, and molecular investigations. Treatment with bromocriptine and pyridoxine showed no improvement. These data support the findings observed among previously reported cohorts that showed poor response of this disease to current regimens. Alternative therapies are needed to ameliorate the clinical complications associated with this disorder.

KEYWORDS: aromatic L-amino acid decarboxylase deficiency, AADC, amino acid decarboxylase, neurotransmitter, dopamine, noradrenaline, serotonin, oculogyric crises

CITATION: Alfadhel and Kattan. Aromatic Amino Acid Decarboxylase Deficiency Not Responding to Pyridoxine and Bromocriptine Therapy: Case Report and Review of Response to Treatment. *Journal of Central Nervous System Disease* 2014:6 1–5 doi: 10.4137/JCNSD.S12938.

RECEIVED: August 4, 2013. **RESUBMITTED:** December 3, 2013. **ACCEPTED FOR PUBLICATION:** December 11, 2013.

ACADEMIC EDITOR: Alexander Rotenberg, Editor in Chief

TYPE: Case report

FUNDING: Author(s) disclose no funding sources.

COMPETING INTERESTS: Author(s) disclose no potential conflicts of interest.

CORRESPONDENCE: dralfadhel@yahoo.com

Introduction

Aromatic L-amino acid decarboxylase (AADC) deficiency (Online Mendelian Inheritance in Man (OMIM® #608643) is an autosomal recessive neurotransmitter disorder.[1–3] It is caused by a deficiency in AADC due to a mutation in the AADC gene (*DDC*) on chromosome 12p12.3-p12.[3,4] This leads to deficiencies in combined monoamines, catecholamines, and serotonin. It is characterized clinically by global developmental delay, truncal hypotonia, oculogyric crises, dystonia, sweating, severe progressive epileptic encephalopathy, and other signs of catecholamine and serotonin deficiencies.[2–5] Diagnosis relies on the presence of a characteristic cerebrospinal fluid (CSF) profile (low homovanillic acid, 5-hydroxyindoleacidicacid, and 3-methoxy-4-hydroxyphenolglycole, as well as elevated 3-O-methyl-L-dopa, L-dopa, and 5-hydroxytryptophan), the absence of plasma AADC activity, or elevated urinary vanillactic acid, and confirmation of the sequencing of the DOPA decarboxylase (DDC) gene.[2,3,6] To date, there is no cure for AADC deficiency, and there are conflicting data in the literature regarding the best treatment options.[7] However, the first-line medications appear to be dopamine agonists, such as bromocriptine combined with pyridoxine.[3,4] We report the case of an 8-month-old boy diagnosed with an AADC deficiency who did not respond to bromocriptine and pyridoxine treatment.

Case Report

An 8-month-old full-term baby (with normal vaginal delivery) born to Saudi first-cousin parents who met appropriate growth

parameters and did not have a significant antenatal history. He was discharged at the second day of life with no complications. The child presented to King Abdulaziz Medical City at 4.5 months of age when he developed a fever and flu-like symptoms, requiring admission to the Pediatric Intensive care Unit for 5 days. On reviewing his clinical history, the parents noticed that he was floppy a few days after birth. In addition, they noticed abnormal posturing of his right lower limbs with eye conversion that last for few minutes, but which recurred frequently at 2 months of age. Furthermore, he demonstrated excessive sweating and difficulties with feeding. His developmental history showed a global developmental delay with poor head control; there was no cooing, no social smile, he did not roll over, and he did not sit. His developmental age was equal to 1 month.

On examination, the growth parameters showed the following: length, 82 cm (50th percentile); weight, 11.07 kg (2nd percentile); and head circumference, 47 cm (50th percentile) with no dysmorphic features or neurocutaneous stigmata. Neurological examination showed: bilateral positive red reflex; not fixing or following; axial hypotonia with peripheral hypertonia; dystonic posture; and hyperreflexia of all limbs. Other systemic examinations demonstrated no significant abnormalities.

Additional diagnostic investigations were unrevealing. Continuous electroencephalogram (EEG) monitoring for 2 days was normal, and it was concluded that these attacks were consistent with occulogyris crises. An echocardiogram was normal. Brain computed tomography (CT) was normal. Brain and spine magnetic resonance imaging (MRI) showed no intracranial abnormality. Auditory brainstem response showed a central defect in the right auditory pathway. The ophthalmologic evaluation was normal.

All the following investigations were also unremarkable: complete blood count, liver enzymes, serum electrolytes and renal function. Biochemical investigations included acylcarnitine profile, plasma aminoacids were unremarkable. Urine organic acids showed moderately elevated homovanillic acid and slight elevation of methylglutaric and methylglutaconic acids.

A neurotransmitter metabolite cerebrospinal fluid (CSF) panel showed reduced concentrations of homovanillic acid 60 nmol/L (403–919 nmol/L) and 5-OH-indolacetic acid 93 nmol/L (170–412 nmol/L), as well as their ratio of 0.6 (1.8–3), and a clearly increased concentration of 3-ortho methyl dopa of 2,076 nmol/L (0–50 nmol/L). The plasma levels of amine neurotransmitter metabolites showed the following: vanillymandelicacid (3.9; 12–73 nmol/L), 3-methoxy-4-hydroxy-phenylglycol (2.4; 9–37 nmol/L) and homovanillic acid (19.3; 43–131 nmol/L) were strongly decreased; while 5-hydroxyindolacetic acid was borderline low (33.1; 21–183 nmol/L). Vanillactic acid (478 nmol/L), which is the metabolite of a dopamine precursor, was strongly increased; this metabolite pattern is fully characteristic of an AADC deficiency. The plasma AADC enzyme activity was 4 pmol/mlMin (47–119 pmol/mlMin) which is clearly reduced. Sequence analysis of the *DDC* gene identified a homozygous missense mutation *c.1234C>T (p. R412W)*. The parents were tested and found to be carriers for this mutation. After the diagnosis was confirmed, the patient was started on pyridoxine at 100 mg orally, every 12 (q12) hours, and bromocriptine at 10 mg orally q12 hours. However, the proband continued to present with agitation and insomnia with no improvement in the duration or frequency of the occulogyris crises. Two months later, the medications were stopped, as the patient did not appear to respond to treatment.

Discussion

AADC deficiency was first described by Hyland and Clayton in 1990, when they reported on male monozygotic twins who presented at the age of 2 months with severe hypotonia and oculogyric crises.[8] Subsequently, AADC deficiency has been reported in almost 80 patients worldwide.[1,3,4] The most consistent features associated with this deficiency are those of combined dopamine and noradrenaline deficiency. The signs of dopamine deficiency include hypokinesia, rigidity, dystonia (with or without diurnal variations), distal chorea, and oculogyric crises. The clinical features of noradrenaline insufficiency include ptosis, miosis, profuse oropharyngeal secretions, postural hypotension, autonomic dysfunction, and temperature instability. Similarly, symptoms of serotonin deficiency include sleep disorders, memory and learning disabilities, and behavioral disturbances.[9] Hypotonia and oculogyric crises are the most common clinical signs noted across all reported patients.[3] The patient presented in this report showed a mixture of these clinical features.

Treatment of AADC deficiency is supportive. The most common first-line treatments are bromocriptine and pyridoxine with dosages ranging between 40 mg/day and 1,800 mg/day (4.0–81 mg/kg/day) and 1.0–45.5 mg/day (0.013–4.0 mg/kg/day), respectively. Bromocriptine is a dopamine receptor agonist with high affinity for D2-like receptors,[4,10] and has been prescribed to correct motor deficit like hypokinesia, axial hypotonia, limb hypertonia, dystonia and choreoathetosis. However, its effect has varied anmong individuals.[4] Pyridoxine or vitamin B_6 is also given to patients to boost residual AADC activity with a cofactor excess.[10] Other medications used in the management of affected children are monoamine oxidase inhibitors such as selegiline, pergolide, tranylcypromine, trihexyphenidyl, L-dopa, and folinic acid.[3,4] Most of the reported patients, as well as current case, showed no response to these therapies (Table 1). However, Brun et al.[3] (2010) presented 15 patients who improved on a combined therapy with pyridoxine, dopamine agonists, and monoamine oxidase B inhibitors.

Gene therapy is a promising experimental approach to AADC deficiency treatment of AADC deficiency, where the *DCC* gene may be transferred directly into patients' cells to

Table 1. Summary of published treatments and clinical responses in AADC deficiency treatment.

ARTICLE, YEAR	PATIENT NO.	M:F	RESPONSE TO PYRIDOXINE	RESPONSE TO BROMOCRIPTINE	ADDITIONAL TREATMENTS	RESPONSE TO ADDITIONAL TREATMENTS
Hyland et al., 1992[2]	2	M	No clinical response	Slight improvement in oculogyric crises	Tranylcypromine Dexamphetamine Imipramine	Tranylcypromine: Improved spontaneous movement and also improved muscle tone Dexamphetamine and Imipramine had no clinical response
Maller et al., 1997[1]	1	M	No clinical response	Partial improvement in muscle tone and head control	Tranylcypromine	Improvement in muscle tone, spontaneous movement and head control
Korenke et al., 1997[5]	1	F	Decrease occulogyris crises and improvement in muscle tone	Improvement in hypokinesia and hypotonia	Levodopa Selegiline	Levodopa: decreased extrapyramidal movement Selegiline: temporarily suppressed occulogyris crises, improve muscle tone and bowel function
Abeling et al., 1998[12]	1	F	NA	NA	NA	NA
Swoboda et al., 1999[13]	2	1:1	No clinical response	Decreased the frequency of oculogyric episodes and rigidity	L-dopa 5-hydroxytryptophan (5-HTP) Pergolide Tranylcypromine Trihexyphenidyl Buspirone Oxymetazoline hydrochloride Pseudoephedrine hydrochloride Sertraline hydrochloride Midodrine hydrochloride	L-dopa: No clinical response 5-HTTP: induced l ethargy and worsened axial hypotonia Pergolide: complete resolution of dystonic spells and oculogyric crises Tranylcypromine: improved coordination and spontaneous movement in one patient Trihexyphenidyl: modestly improved tone, limb rigidity, and excessive sweating Buspirone: reduced limb rigidity and irritability initially, then, led to tardive dyskinesia Others: no significant clinical response
Fiumara et al., 2002[14]	2	M	Partial clinical improvement initially then deteriorate over time	Partial clinical improvement initially then deteriorated over time	Selegiline L-dopa 5-HTTP Cabergoline	Selegiline, L-dopa and 5-HTTP: Slight clinical improvement initially then deteriorate over time Cabergoline: no clinical response
Chang et al., 2004[15]	3	2:1	NP	NP	Levodopa/carbidopa	Marked clinical improvement initially but it deteriorated over time
Pons et al., 2004[4]	6	3:3	3/6 no clinical response, rest are favorable	3/6 slight improvement	Tranylcypromine Melatonine Pergolide	Tranylcypromine and pergolide: 3/6 favorable and rest no clinical response Melatonin: improvement in sleep pattern
Tay et al., 2007[16]	2	F	Partial clinical improvement	Slight clinical improvement	Selegiline	Improved muscle strength
Ito et al., 2008[17]	1	M	Partial improvement in vocalization and voluntary movement	Partial improvement in vocalization and voluntary movement	Valproic acid clobazam	Seizure reduction

(*Continued*)

Table 1. (*Continued*)

ARTICLE, YEAR	PATIENT NO.	M:F	RESPONSE TO PYRIDOXINE	RESPONSE TO BROMOCRIPTINE	ADDITIONAL TREATMENTS	RESPONSE TO ADDITIONAL TREATMENTS
Manegold et al., 2009[7]	9	6:3	4/9 with slight improvement	2/9 with slight improvement, other, deteriorated after discontinuation of therapy	Selegiline, tranylcypromine L-dopa Pergolide	Selegiline: used in 3/9 One patient improved temporarily, others deteriorated Tranylcypromine: used in 2/9, one deteriorate and one improved L-dopa: 6/9, three improved and three showed no clinical response Pergolide: 1/9, no clinical response
Lee et al., 2009[18]	8	4:4	No clinical response	No clinical response	Moclobemide Akineton	Moclobemide: 2/9, mild improvement in the duration of oculogyric crises and irritability Akineton: 3/9, no response
Brun et al., 2010[3]	78	41:31	15/55 good clinical response, rest are no clinical response	15/38 good clinical response, rest are no clinical response	Selegiline L-dopa Pergolide Tranylcypromide Trihexyphenidyl	Selegiline: 19/78 L-dopa: 10/78 Pergolide : 12/78 Tranylcypromide: 22/78 Trihexyphenidyl: 15/78 All had no clinical response
Hwu et al., 2012[11]	4	1:3	NA	NA	Gene therapy	Weight gain and improved motor function
Alfadhel and Kattan, 2013	1	M	No clinical response	No clinical response	NP	NP

Note: *given in combination with other drugs.
Abbreviations: M, male; F, female; NA, not available; NP, not prescribed.

stabilize the expression of the AADC protein.[10] The feasibility of gene therapy for AADC deficiency is underscored by a recent report of functional motor improvement in four children with AADC deficiency. Here, Hwu et al. applied the adeno-associated virus type 2 vector to deliver the *DCC* gene to the putamen area, without complications.[11]

Conclusion

We alert clinicians to consider AADC deficiency in any infant with hypotonia and oculogyric crises. We note that despite the poor clinical response to current medications, gene therapy shows promise as a treatment for this disorder.

Acknowledgments

We are grateful to the patient and his family reported in this article for their genuine support. We also thank Dr. Alexander Rotenberg for editing the manuscript.

Author Contributions

Wrote the first draft of the manuscript: MAF, RK. Contributed to the writing of the manuscript: MAF, RK. Agree with manuscript results and conclusions: MAF, RK. Jointly developed the structure and arguments for the paper: MAF, RK. Made critical revisions and approved final version: MAF. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

REFERENCES

1. Maller A, Hyland K, Milstien S, Biaggioni I, Butler IJ. Aromatic L-amino acid decarboxylase deficiency: clinical features, diagnosis, and treatment of a second family. *J Child Neurol*. Sep 1997;12(6):349–54.
2. Hyland K, Surtees RA, Rodeck C, Clayton PT. Aromatic L-amino acid decarboxylase deficiency: clinical features, diagnosis, and treatment of a new inborn error of neurotransmitter amine synthesis. *Neurology*. Oct 1992;42(10): 1980–8.
3. Brun L, Ngu LH, Keng WT, et al. Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. *Neurology*. July 6, 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*. April 13, 2004;62(7):1058–65.
5. Korenke GC, Christen HJ, Hyland K, Hunneman DH, Hanefeld F. Aromatic L-amino acid decarboxylase deficiency: an extrapyramidal movement disorder with oculogyric crises. *Eur J Paediatr Neurol*. 1997;1(2–3):67–71.

6. Hyland K, Clayton PT. Aromatic L-amino acid decarboxylase deficiency: diagnostic methodology. *Clin Chem*. Dec 1992;38(12):2405–10.
7. 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*. Jun 2009;32(3):371–80.
8. Hyland K, Clayton PT. Aromatic amino acid decarboxylase deficiency in twins. *J Inherit Metab Dis*. 1990;13(3):301–4.
9. Grattan-Smith PJ, Wevers RA, Steenbergen-Spanjers GC, Fung VS, Earl J, Wilcken B. Tyrosine hydroxylase deficiency: clinical manifestations of catecholamine insufficiency in infancy. *Mov Disord*. Mar 2002;17(2):354–9.
10. Allen GF, Land JM, Heales SJ. A new perspective on the treatment of aromatic L-amino acid decarboxylase deficiency. *Mol Genet Metab*. May 2009;97(1):6–14.
11. Hwu WL, Muramatsu S, Tseng SH, et al. Gene therapy for aromatic L-amino acid decarboxylase deficiency. *Sci Transl Med*. May 16, 2012;4(134):134ra161.
12. Abeling NG, van Gennip AH, Barth PG, van Cruchten A, Westra M, Wijburg FA. Aromatic L-amino acid decarboxylase deficiency: a new case with a mild clinical presentation and unexpected laboratory findings. *J Inherit Metab Dis*. Jun 1998;21(3):240–2.
13. Swoboda KJ, Hyland K, Goldstein DS, et al. Clinical and therapeutic observations in aromatic L-amino acid decarboxylase deficiency. *Neurology*. October 12, 1999;53(6):1205–11.
14. Fiumara A, Brautigam C, Hyland K, et al. Aromatic L-amino acid decarboxylase deficiency with hyperdopaminuria. Clinical and laboratory findings in response to different therapies. *Neuropediatrics*. Aug 2002;33(4):203–8.
15. Chang YT, Sharma R, Marsh JL, et al. Levodopa-responsive aromatic L-amino acid decarboxylase deficiency. *Ann Neurol*. Mar 2004;55(3):435–8.
16. Tay SK, Poh KS, Hyland K, et al. Unusually mild phenotype of AADC deficiency in 2 siblings. *Mol Genet Metab*. Aug 2007;91(4):374–8.
17. Ito S, Nakayama T, Ide S, et al. Aromatic L-amino acid decarboxylase deficiency associated with epilepsy mimicking non-epileptic involuntary movements. *Dev Med Child Neurol*. Nov 2008;50(11):876–8.
18. Lee HF, Tsai CR, Chi CS, Chang TM, Lee HJ. Aromatic L-amino acid decarboxylase deficiency in Taiwan. *Eur J Paediatr Neurol*. Mar 2009;13(2):135–40.