

Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency



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ABSTRACT

Objective: To describe the current treatment; clinical, biochemical, and molecular findings; and clinical follow-up of patients with aromatic L-amino acid decarboxylase (AADC) deficiency.

Method: Clinical and biochemical data of 78 patients with AADC deficiency were tabulated in a database of pediatric neurotransmitter disorders (JAKE). A total of 46 patients have been previously reported; 32 patients are described for the first time.

Results: In 96% of AADC-deficient patients, symptoms (hypotonia 95%, oculogyric crises 86%, and developmental retardation 63%) became clinically evident during infancy or childhood. Laboratory diagnosis is based on typical CSF markers (low homovanillic acid, 5-hydroxyindoleacetic acid, and 3-methoxy-4-hydroxyphenolglycol, and elevated 3-O-methyl-L-dopa, L-dopa, and 5-hydroxytryptophan), absent plasma AADC activity, or elevated urinary vanillic acid. A total of 24 mutations in the *DDC* gene were detected in 49 patients (8 reported for the first time: p.L38P, p.Y79C, p.A110Q, p.G123R, p.I42fs, c.876G>A, p.R412W, p.I433fs) with IVS6+4A>T being the most common one (allele frequency 45%).

Conclusion: Based on clinical symptoms, CSF neurotransmitters profile is highly indicative for the diagnosis of aromatic L-amino acid decarboxylase deficiency. Treatment options are limited, in many cases not beneficial, and prognosis is uncertain. Only 15 patients with a relatively mild form clearly improved on a combined therapy with pyridoxine (B6)/pyridoxal phosphate, dopamine agonists, and monoamine oxidase B inhibitors. *Neurology*® 2010;75:64–71

GLOSSARY

5HIAA = 5-hydroxyindoleacetic acid; **AADC** = aromatic L-amino acid decarboxylase; **HVA** = homovanillic acid; **MAO-A** = monoamine oxidase A; **MET** = metanephrine; **MHPG** = 3-methoxy-4-hydroxyphenylglycol; **PLP** = pyridoxal phosphate; **VLA** = vanillic acid.

Aromatic L-amino acid decarboxylase (AADC) deficiency (OMIM 107930) is an inborn error of neurotransmitter biosynthesis with an autosomal recessive inheritance.^{1,2} Mutations in the gene encoding for the enzyme AADC (*DDC*) lead to a severe combined deficiency of serotonin and catecholamines,³ clinically characterized by vegetative symptoms, oculogyric crises, dystonia, and severe neurologic dysfunction in infancy.^{4–6} Serotonin and dopamine are formed following the hydroxylation of tryptophan and tyrosine by tryptophan and tyrosine hydroxylases and by a subsequent decarboxylation of the corresponding intermediates 5-hydroxytryptophan and L-dopa by a pyridoxal phosphate (PLP)-dependent AADC (figure 1).⁷

The exact diagnosis of AADC deficiency relies on the analysis of neurotransmitters and their metabolites in CSF; however, urinary vanillic acid (VLA) is also highly diagnostic.^{8–11} Measurement of AADC activity in plasma and *DDC* gene sequencing are essential for the final diagnosis.^{3,8,12}

The therapy is aimed at correcting the neurotransmitter abnormalities, offering the following medications: dopamine receptor agonists, anticholinergics, monoaminoxidase inhibitors, α -adrenergic agonists, selective serotonin reuptake inhibitors, therapeutic doses of the cofactor

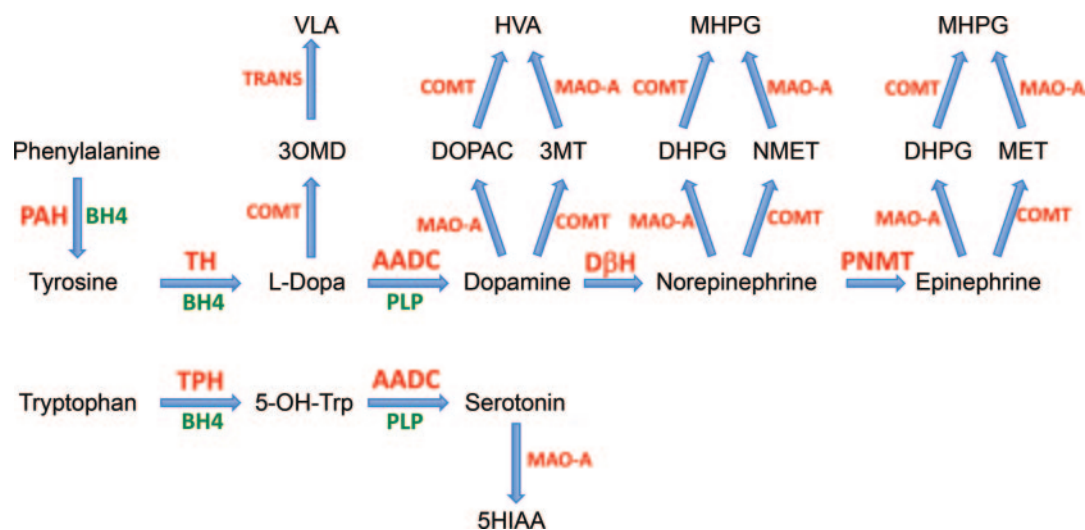
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Figure 1 Biosynthesis and metabolism of catecholamines and serotonin



Enzymes and abbreviations: AADC = aromatic L-amino acid decarboxylase; COMT = catechol-O-methyltransferase; D β H = dopamine- β -hydroxylase; MAO-A = monoamine oxidase A; PAH = phenylalanine-4-hydroxylase; PNMT = phenylethanolamine N-methyltransferase; TH = tyrosine-3-hydroxylase; TPH = tryptophan-5-hydroxylase; TRANS = transaminase. Reactions catalyzed by MAO-A are coupled with an additional step catalyzed by either aldehyde or aldose dehydrogenase (catabolism of dopamine and serotonin; not shown) or aldehyde or aldose reductase (catabolism of norepinephrine and epinephrine; not shown). Metabolites and abbreviations: 3MT = 3-methoxytryptamine; 3OMD = 3-O-methyldopa; 5-OH-Trp = 5-hydroxytryptophan; 5HIAA = 5-hydroxyindoleacetic acid; DHPG = 3,4-dihydroxyphenylglycol; DOPAC = 3,4-dihydroxyphenylacetic acid; HVA = homovanillic acid; L-dopa = 3,4-dihydroxyphenylalanine; MET = metanephrine; MHPG = 3-methoxy-4-hydroxyphenylglycol; NMET = normetanephrine; VLA = vanillic acid. Cofactors and abbreviations: BH4 = tetrahydrobiopterin; PLP = pyridoxal phosphate.

of AADC (pyridoxine or PLP), catechol-O-methyltransferase inhibitor, precursors of dopamine and serotonin (L-dopa, 5-OH-Trp), folic acid, and melatonin. Response to treatment varies, but in many cases the therapy shows no or little benefit.¹³⁻²²

In this article, we summarize the biochemical and molecular findings and the course of the disease in 78 patients with AADC deficiency tabulated in the international JAKE database (http://www.biopku.org/BioPKU_Databases/JAKE.asp).

METHODS Biochemical investigations. Neurotransmitter metabolites in CSF were investigated by high-performance liquid chromatography with electrochemical detection, with slight modifications in different laboratories, but essentially as described elsewhere.²³ VLA was investigated by a standard method for organic acids profile in urine.²³

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all patients or their physicians who participated in this study. No approval was required from the regional ethical committees. All biochemical and clinical data were collected within the routine diagnostic procedures.

Case reports. The age at diagnosis ranged from 4 months to 24 years (median 3.9 years) and was available from 60 of 78

patients. Twenty patients were diagnosed at the Children's Hospital in Zürich.

A questionnaire with the following sections was distributed to physicians managing AADC-deficient patients: 1) general patient information, 2) birth information and laboratory tests, 3) clinical information with signs and symptoms and treatment protocols, 4) EEG/CT/MRI data, 5) DNA analysis, and 6) follow-up information. A written consensus was provided for all submitted data by physicians.

A literature search was conducted using MEDLINE (1990–August 2009) for the following key words: aromatic L-amino acid decarboxylase, monoamine decarboxylase, dopa decarboxylase, AADC, and DDC.

Detailed information on AADC-deficient patients is tabulated in the JAKE database (<http://www.biopku.org>). Clinical information is summarized in table 1, biochemical and molecular data in table e-2 on the *Neurology*[®] Web site at www.neurology.org, and therapy in table 2. Detailed information on DNA variations is available from the BIOMDB database (<http://www.biopku.org>). Most important information is included in the case reports (table e-1).

RESULTS Signs and symptoms. All patients showed symptoms typical for deficiency of catecholamines and serotonin. In 96% of them, symptoms became clinically evident during infancy (≤ 18 months) or during childhood (≤ 10 years). Only 6 patients were clinically conspicuous at adolescence or adulthood.

Almost all patients (95%) presented with muscular hypotonia. Episodes of oculogyric crises were doc-

Table 1 Most common signs and symptoms in patients with AADC deficiency

Symptoms ^a	%	All patients	Infancy, ≤18 mo	Childhood, ≤10 y	Adolescence, ≥11 y	Adulthood
Characteristic features						
Hypotonia	95	74/78	35/38	33/33	3/4	3/3
Oculogyric crises	86	67/78	33/38	28/33	3/4	3/3
Other neurologic signs						
Sweating	65	51/78	20/38	26/33	2/4	3/3
Developmental retardation	63	49/78	22/38	24/33	1/4	2/3
Dystonia	53	41/78	21/38	16/33	1/4	2/3
Hypertonia	44	35/78	14/38	18/33	1/4	2/3
Feeding/swallowing difficulties	42	33/78	17/38	16/33	0/4	0/3
Dysarthria/speech difficulties	41	32/78	9/38	20/33	1/4	2/3
Hypersalivation	41	32/78	12/38	17/33	1/4	2/3
Ptosis	39	30/78	18/38	10/33	2/4	0/3
Insomnia	37	29/78	11/38	17/33	1/4	0/3
Irritability	35	27/78	12/38	12/33	1/4	2/3
Hypokinesia	32	25/78	8/38	14/33	1/4	2/3
Nasal congestion	31	24/78	10/38	12/33	2/4	0/3
Temperature instability	29	23/78	12/38	9/33	1/4	1/3
Poor head control	28	22/78	10/38	9/33	2/4	1/3
Athetosis	27	20/78	8/38	11/33	0/4	1/3
Poor eye fixation	26	19/78	10/38	9/33	0/4	0/3
Chorea	22	17/78	7/38	9/33	1/4	0/3
Brain imaging						
Abnormal MRI	24	19/78				
Abnormal EEG	13	10/78				
Abnormal CT	6	5/78				

Abbreviation: AADC = aromatic L-amino acid decarboxylase.

^a For the full list of signs and symptoms and description of radiologic findings, see table e-1 and online information in the JAKE database (<http://www.biopku.org>).

umented in 86% of patients at the time of investigation. Thus, oculogyric crises and hypotonia can be considered characteristic features of AADC deficiency (table 1). A total of 63% of the patients developed developmental retardation: mental or motor retardation or both. Additional autonomic symptoms such as excessive sweating or temperature instability occurred in 65% and 29% of the patients. Further, most frequent symptoms described were feeding or speech difficulties (42%) and movement disorders like athetosis (27%), chorea (22%), dystonia (53%), or hypokinesia (32%). Poor eye fixation was documented in 19 patients (26%), poor head control in 22 patients (28%), hypersalivation in 32 patients (41%), and hypertonia in 35 patients (44%). A total of 37% of the patients had insomnia and 35% had irritability. In 24 patients (31%), nasal congestion was reported, and in 30 patients (39%), ptosis was evident (table 1).

For more detailed information, see table e-1 or the JAKE database (<http://www.biopku.org>).

Biochemical investigations. The age at laboratory diagnosis varied from 4 months to 24 years (median 3.9 years). None of the patients was diagnosed in the neonatal period. The results of the CSF, plasma, and urine analyses at the time of diagnosis are shown in table e-2. All patients whose biochemical data are reported showed significantly reduced 5-hydroxyindoleacetic acid (5HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in CSF together with elevations of 5-OH-Trp and 3-O-methyl-dopa (3OMD). In all patients in whom AADC activity in plasma was measured, it was always very low or not detectable. VLA elevation in urine was reported in a few cases and in some elevation was rather mild. L-dopa (3,4-dihydroxyphenylalanine) was, however, normal in 6 out of 78 patients. A typical pattern of CSF metabolites is summarized in figure 2.

Genotypes. We found a wide range of mutations and genotypes (table e-2 and figure e-1), and DNA analysis was available in 49 out of 78 patients. Out of 30 mutations described in the BIOMDB database, 24 different mutations were detected in patients from the JAKE database, of which 8 had not been described earlier (p.L38P, p.Y79C, p.A110Q, p.G123R, p.I42fs, c.876G>A, p.R412W, p.I433fs). In 3 patients (ID#36, ID#37, ID#48), mutations were found on 1 allele only. The substitution mutation in Intron 6, IVS6+4A>T, was by far the most common mutation (allele frequency 45%), followed by p.S250F (allele frequency 10%), p.G102S (allele frequency 8%), and p.R462P (allele frequency 6%). It is conspicuous that all patients with an IVS6+4A>T mutation are of Chinese or Taiwanese origin and 7 patients whose ethnic origin is not known are living in Taiwan. All the other mutations are presented with allele frequency of 1%–3%. The 3 most common genotypes are IVS6+4A>T/IVS6+4A>T (35%), p.S250F/p.S250F (6%), and p.G102S/p.G102S (4%).

Neuroimaging and EEG investigations. A total of 24% of patients showed an abnormal MRI, 13% an abnormal EEG, and 6% an abnormal CT (table 1). The patients with an abnormal EEG mostly showed slow or rapid activity or polyspikes. Patients with abnormal MRI or CT presented with cerebral atrophy, degenerative changes of the white matter, thinning of corpus callosum, prominent ventricular bodies, leukodystrophy-like pattern, or hypomyelination.

Treatment. Although a variety of medications have been used in patients with AADC deficiency, some therapeutic protocols are used more frequently and

Table 2 Summary of the most frequently used medications in patients with AADC deficiency and recommended treatment modalities

Medication	Dosage reported in JAKE database	No. of patients	%	Starting dosage, ^a mg/kg/d	Dose per day ^a	Maximal dosage, ^a mg/kg/d
Pyridoxine (B6) ^b	40–1,800 mg/d or 4.0–81 mg/kg/d	55/78	71	50	3	200
Bromocriptine ^b	1.0–45.5 mg/d or 0.013–4.0 mg/kg/d	38/78	49	0.25	3	0.5
Pergolide ^b	0.3–1.5 mg/d or 0.006–0.75 mg/kg/d	12/78	15	0.006	2–3	0.05
Selegiline	0.1–6.0 mg/d or 0.03–1.5 mg/kg/d	19/78	24	0.1	2–3	0.3
Tranlycypromide	1.5–54 mg/d or 0.4–0.5 mg/kg/d	22/78	28	0.1	2	0.5
Trihexyphenidyl	0.231–4.62 mg/d or 0.3–0.5 mg/kg/d	15/78	19	0.1	3	0.5
L-Dopa	400–2,250 mg/d or 11.2–54 mg/kg/d	10/78	13	1	3	15

Abbreviation: AADC = aromatic L-amino acid decarboxylase.

^a Modified according to Hoffmann and Surtees.³⁰

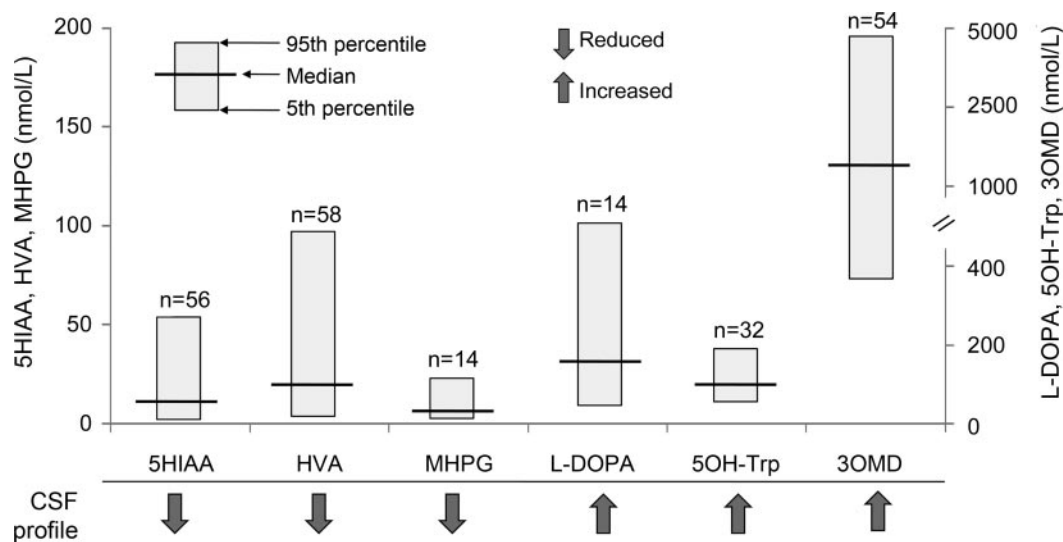
^b Therapy is usually initiated with a combination of the low-dosage pyridoxine and one of the dopamine agonists (bromocriptine or pergolide). In a second step, monoamine oxidase inhibitor is added (e.g., selegiline). All other medications are added only if the initial treatment protocol fails to improve neurologic symptoms.

pyridoxine is the most common drug used (71% of patients). The dosage reported varied between 40 and 1,800 mg/day (4.0–81 mg/kg/day). Bromocriptine was used in 38 out of 78 patients, with a dosage of 1.0–45.5 mg/day (0.013–4.0 mg/kg/day), and tranlycypromide (1.5–54 mg/day or 0.4–0.5 mg/kg/day) and selegiline (0.03–1.5 mg/kg/day) were applied in 28% and 24% of patients. A total of 19% of patients had a therapeutic trial with trihexyphenidyl with dosages of 0.231–4.62 mg/day (0.3–0.5 mg/kg/day), 15% were tried on pergolide (0.3–1.5 mg/day or 0.006–0.75 mg/kg/day), and 13% of patients were treated with L-dopa (400–2,250 mg/day or 11.2–54 mg/kg/day). The majority of cases showed

no or poor response despite different protocols and a combination of different drugs. Only 15 patients (nos. 10, 13, 14, 15, 26, 27, 45, 47, 53, 55, 56, 64, 66, 67, and 71) were reported with good or very good clinical benefit (improvement in at least 5 symptoms). Patients 1–3 have been previously described with favorable clinical benefit,⁶ and 2 other patients (26 and 27) with an excellent response to MAO inhibitor and dopamine agonist therapy.²⁰ There was no significant difference between 2 groups (responder and nonresponder) with regard to biochemical and genetic data.

A total of 73 patients (96%) were clinically inconspicuous before the age of 10 years and most of them

Figure 2 CSF metabolites



CSF concentrations (median and 5th–95th percentile) of key neurotransmitter metabolites in patients with aromatic L-amino acid decarboxylase deficiency at the time of diagnosis. 3OMD = 3-O-methyldopa; 5HIAA = 5-hydroxyindoleacetic acid; 5OH-Trp = 5-hydroxytryptophan; HVA = homovanillic acid; L-dopa = 3,4-dihydroxyphenylalanine; MHPG = 3-methoxy-4-hydroxyphenylglycol. For reference ranges, see table e-2. These may differ between laboratories.

were started on medication immediately after diagnosis. Many of these patients also developed additional non-neurologic symptoms such as ptosis, excessive sweating, temperature instability, and nasal congestion (table 1).

DISCUSSION In this study, we documented clinical, biochemical, and molecular data of 78 patients with AADC deficiency, tabulated in the JAKE database of pediatric neurotransmitter disorders. A total of 32 cases have not been published previously. The clinical presentation of these new patients is in line with the clinical picture of AADC deficiency described in the literature.^{2,5,6,18,24,25} The most frequent neurologic signs and symptoms were muscular hypotonia and oculogyric crises and approximately half of the patients showed movement disorders with hypokinesia, dystonia, athetosis, and chorea. While hypotonia is a rather nonspecific feature, oculogyric crises are typical for AADC-deficient patients and were not present or not reported at the age of investigation in only 11 patients.^{14,25,26} Seven previously unreported cases (49, 52, 53, 60, 61, 63, and 74) also did not present with oculogyric crises at the age of investigation (5 months–11.5 years); however, it is possible that some of these patients will develop such episodes in the future, particularly since some of them were not on treatment. A total of 49 patients were reported with mental or motor retardation.

In general, most of the signs and symptoms described in patients with AADC deficiency can be assigned to deficiencies of dopamine, norepinephrine, epinephrine, and serotonin. Dopamine is synthesized in substantia nigra, ventral tegmentum, and hypothalamus, and its deficiency affects voluntary movements, cognitive function, and emotion, but also hormonal-related functions. Norepinephrine and epinephrine deficiency affects attention, mood, sleep, cognition, and stress hormones, and disturbance in serotonin biosynthesis affects appetite, sleep, memory, learning, body temperature, mood, cardiovascular function, and endocrine functions. Consequently, AADC-deficient patients present with parkinsonism and dystonia, motor activity, and sleep problems (dopamine functions); autonomic dysfunction, temperature instability, and ptosis (norepinephrine and epinephrine function); and sleep disorders, memory and learning disability, and behavioral disturbance (serotonin functions).²⁷

Brain imaging and EEG revealed normal findings in most patients. Ten patients had an abnormal EEG, mostly showing slow or rapid activity or polyspikes.^{4,14,18,19,28} Five patients with an abnormal brain CT and 19 patients with an abnormal MRI presented with cerebral atrophy, degenerative changes

of the white matter, thinning of corpus callosum, prominent ventricular bodies, leukodystrophy-like pattern, hypomyelination, or adult pattern of myelination.^{2,14,19,22,25,28,29}

The clinical phenotype, although quite typical in classic patients, will hardly ever be recognized as AADC deficiency due to its rarity, physicians thus being unfamiliar with the disorder. In general, the results of biochemical investigations will point to AADC deficiency as the underlying cause in a child with a complex neurologic disorder. Laboratory protocol for the diagnosis of AADC deficiency includes investigation of metabolites of dopamine and serotonin (HVA, MHPG, L-dopa, 3OMD, 5-OH-Trp, and 5HIAA) in CSF,⁸ AADC activity in plasma,³ and organic acids (VLA) in urine.¹⁹ Although measurement of VLA within the organic acids profile would be the most practical approach in the diagnosis of AADC deficiency, a number of patients who we investigated presented with only mildly elevated concentrations of urinary VLA (data not shown). Measurement of additional metabolites in urine such as vanilpyruvic acid and N-acetyl-vanilalanine, both metabolites of VLA, may increase the sensitivity of this approach.¹⁹ Thus, CSF investigation of neurotransmitter metabolites is essential for the diagnosis. As shown in table e-2 and figure 2, all patients whose biochemical data are known presented with a typical pattern of metabolites in CSF, specifically reduced concentrations of HVA, 5HIAA, and MHPG, and an elevation of 3OMD, L-dopa, and 5-OH-Trp. L-dopa was reported as elevated in 40 out of 78 patients. In 32 patients, it was not measured (nos. 1, 9, 11, 12, 14, 16–20, 26–35, 48, 49, 58–63, 70, and 75–78), and in patients 13, 53, 69, and 71–73, it was normal. Some variability in the biochemical data could, however, relate to diurnal variation. If there is diurnal variation, then any correlation between treatment response and biochemical data could be obscured by this variation.

In 49 patients, mutation analysis of the *DDC* gene was performed. Different point mutations were identified; 8 mutations have not previously been reported in AADC-deficient patients (p.L38P, p.Y79C, p.A110Q, p.G123R, p.I42fs, c.876G>A, p.R412W, p.I433fs). With the exception of patients with Chinese origin with a common splice mutation IVS6+4A>T, most patients harbor private mutations spread out through the entire *DDC* gene (table e-2). There is no indication for a genotype–phenotype correlation.

The therapy is aimed at correcting the neurotransmitter abnormalities, especially those of serotonin and catecholamines. Unfortunately, a substitution therapy with neurotransmitter precursors L-dopa and 5-

hydroxytryptophan is not effective in nearly all AADC-deficient patients, as they cannot be further metabolized and in fact already circulate in enormous amounts. Nevertheless, 3 siblings responded dramatically to L-dopa. They carry a homozygous mutation affecting the binding of the substrate L-dopa to the enzyme.⁵ Thus, treatment strategies are aiming either at an augmentation of residual AADC activity with pyridoxine and PLP or the use of MAO-B inhibitors and dopamine agonists are commonly used.

Patients received dopamine receptor agonists, anticholinergics, monoaminoxidase inhibitors, α -adrenergic agonists, selective serotonin reuptake inhibitors, cofactor of AADC (pyridoxine or PLP), catechol-*O*-methyltransferase inhibitors, precursors of dopamine and serotonin (L-dopa, 5-OH-Trp), L-dopa decarboxylase inhibitors, folinic acid, and melatonin. Other medications were used to lesser degree. The overall response to drug therapy was good in 15 patients, with unsatisfactory or no response in the other 63 patients. There may be a difference in response to treatment between male and female patients, as reported by Pons et al.⁶ Ten out of the 15 patients with a satisfactory clinical benefit were male. However, more male than female patients were investigated. There were 41 male patients, 31 female patients, and 6 patients with unknown sex who took part in our study. The 15 patients with a good clinical response still have different symptoms that never completely resolved.

First-choice medications appear to be dopamine agonists such as bromocriptine or pergolide in combination with pyridoxine, and MAO inhibitors such as selegiline in the second step (table 2). Bromocriptine is usually given at a starting dosage of 0.25 mg/kg/day divided in 3 doses per day. Another dopamine agonist, pergolide, should be given at a very low starting dosage of 0.006 mg/kg/day twice a day. Beneficial effect of pergolide was described in patients with a severe neurotransmitter deficiency due to tetrahydrobiopterin deficiency. Alternatively to selegiline, tranylcypromine can be given in 1–3 doses a day at a dosage around 8 mg/day. **The therapy with trihexyphenidyl should start at a dosage of 0.03 mg/kg per day, divided in 3 doses. The dosage should then be increased by 0.03 mg/kg per day each week until the child shows any improvement, the child develops side effects, or a limit of 0.5 mg/kg per day is reached. In adolescents and adults, total daily doses exceeding 15 mg should be used with caution. [Boldface text has been corrected per erratum.]** As alternative therapy, L-dopa may be given. L-dopa should be given 3 times a day at a dosage of ≤ 15 mg/kg/day. L-dopa should be increased in steps of not more than 1 mg/kg over days, weeks, or sometimes several months. It should be introduced slowly because of receptor hypersensitivity in early-diagnosed severe cases, and start at very low doses given up to 6 times a day. In late-diagnosed severe cases, patients maximally tolerate

a dose of up to 10 mg/kg/day, which should be given for 6 months before deciding whether it is beneficial or not. Additional carbidopa treatment should be avoided, because of a possible deterioration of symptoms. Pyridoxine, precursor of the natural cofactor of AADC, should not be given at doses of >200 mg/kg/day.³⁰ Pyridoxine is first phosphorylated to pyridoxine 5'-phosphate and subsequently converted to PLP. There is evidence that an optimal level of PLP is important for AADC stability and that PLP may be required for the maintenance of AADC activity.¹³

Folinic acid substitution in AADC-deficient patients is recommended at a dosage of 10–20 mg/day because of possible cerebral folate depletion due to methylation of accumulated L-dopa.

Drug therapy in patients with AADC deficiency is a challenge and unfortunately there are still no good therapeutic strategies available. For many patients, the overall outcome is disappointing.

There is a new hope that AADC-deficient patients may benefit from gene therapy in the future. By delivering the human *DCC* gene into patients' cells,¹³ this technique may stabilize expression of a functional AADC protein. Similar attempts are in progress for patients with Parkinson disease.³¹ In a phase I safety trial, patients with moderate to advanced Parkinson disease received bilateral infusion of a low dose of the adeno-associated viral hAADC vector into the putamen. This gene therapy approach has been well-tolerated and shows evidence of sustained gene expression.

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