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CASE REPORT

Report of Two Never Treated Adult Sisters with Aromatic L-Amino Acid Decarboxylase Deficiency: A Portrait of the Natural History of the Disease or an Expanding Phenotype?

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Abstract Two sisters were diagnosed in their adulthood with aromatic L-amino acid decarboxylase (AADC) deficiency (OMIM#608643). They experienced early myasthenia-like manifestations, myoclonic jerks, oculogyric crises, tremors, and developmental delay during childhood; clinical stabilization afterwards; and spontaneous improvement during adolescence and young adulthood. Two novel pathogenic mutations on *DDC* gene [p.Tyr37Thrfs*5 (c.105delC) and p. F237S (c.710 T>C)] were associated with undetectable enzyme activity in plasma and only a mild reduction of biogenic amines in cerebrospinal fluid (CSF). The increase of both 3-*O*-methyldopa and 5-hydroxytryptophan on CSF was the most relevant biochemical alteration denoting AADC defect in these subjects. Transdermal rotigotine remarkably improved their gross motor functions and the asthenic status they complained. The present cases broaden the phenotypic spectrum of AADC deficiency and suggest that (1) AADC defect is not a progressive neurological disease and behaves rather as a neurodevelopmental disorder that improves during the second decade of life; (2) treatment-naïve adults can still respond well to neurotransmitter therapy; and (3) the possibility of a mild presentation of AADC deficiency should be considered when examining young adults with asthenic and parkinsonian symptoms.

Introduction

Aromatic L-amino acid decarboxylase (AADC) deficiency (OMIM#608643) is a rare and severe disorder of biogenic amine synthesis (Hyland et al. 1992; Brun et al.

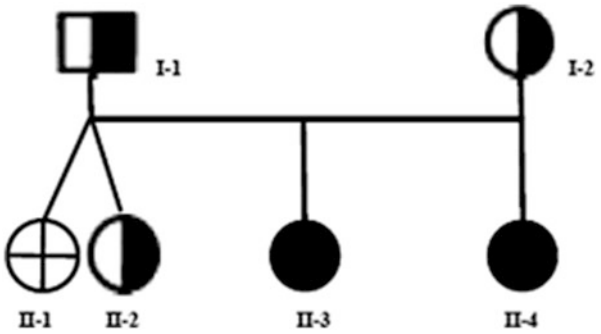

Fig. 1 Pedigree of the family

2010). Unlike other congenital defects of biogenic amine metabolism, no exhaustive data are available on the natural history of the disease and the efficacy of treatments during adulthood (Segawa 2011). Reported here is a novel family, whose follow-up lasted over than 30 years, demonstrating that treatment-naïve adults with AADC deficiency can respond remarkably well to therapy.

Patients

Figure 1 shows the pedigree, of the family, which includes two unrelated healthy Italian parents (Fig. 1: I-1 and I-2), two sisters with AADC deficiency [Fig. 1: II-3 (Patient 1) and II-4 (Patient 2)], and a heterozygote eldest sister (Fig. 1: II-2) (see below for genetic analysis). This last subject, a 35-year-old woman, was born after a complicated twin pregnancy (her sister was stillborn – Fig. 1: II-1; clinical details are not available) and soon after birth suffered from epileptic seizures and non-epileptic oculogyric crises. Later in childhood, she was diagnosed as affected by severe cerebral palsy and intellectual disability. Upon her most recent examination, at the age of 34, she showed microcephaly, profound mental disability, and severe spastic-dystonic tetraparesis with dystonic scoliosis.

Patient 1 (Fig. 1; II-3)

This 33-year-old female was born from an emergency cesarean section after a pregnancy with reduced fetal movements. At birth, she was floppy and weak. Multifocal myoclonic jerks, oculogyric crises, occasional palpebral ptosis, and tremors of upper limbs emerged over the following months. She sat unaided after the age of 3, stood up at 5, and walked unaided at 7. She had never been able to run. A diurnal fluctuation of weakness and fatigability was constantly recorded since early childhood. Mental and language development were impaired, and she attained a secondary school degree with educational support. By the age of 15, oculogyric crises disappeared. Because of her persisting marked weakness and easy fatigability, at the age of 17, she underwent single-fiber electromyography (EMG), which suggested a defect of neuromuscular transmission of congenital myasthenia type. Even though anti-acetylcholine receptor (AChR) antibodies and mutations of a panel of AChR genes subunits yielded negative results, she went under 3,4 diaminopyridine (DAP) (10 mg/4 times a day) for 4 years with transient improvements of weakness, motor performances, and speech. At the age of 20, she experienced irregular menstrual cycles: specific investigations revealed hyperprolactinemia with normal brain MRI. She was rehospitalized at the age of 32 because of increasing focal jerks. Upon examination, she appeared as a friendly and talkative woman with borderline cognitive impairment (WAIS-R total IQ = 74; verbal IQ = 78; performance IQ = 72), fluctuating palpebral ptosis and muscular weakness, clumsy gait and mild derangement of postural reactions, nasal speech, spontaneous multifocal myoclonic jerks mainly at the upper limbs, hypo- and bradykinesia, brady-palilalia, and occasional dystonic postures of the hands.

Patient 2 (Fig. 1; II-4)

This 23-year-old female presented with a severe motor developmental delay, muscular weakness, hypotonia, and recurrent non-epileptic focal jerks since birth. Bilateral fluctuating palpebral ptosis became evident at the age of 5 months. She was not able to walk unsupported until the age of 5. She experienced frequent oculogyric crises, often precipitated by tiredness and a myasthenia-like phenotype milder than patient 1. Notwithstanding some learning difficulties, she reached a secondary school educational level with special teaching support. She suffered from headache and orthostatic hypotension since adolescence. Hyperprolactinemia was detected at the age of 17. Upon examination at the age of 22, she showed mild dysarthria, bradylalia, fluctuating palpebral ptosis, multifocal myoclonic jerks, orthostatic hypotension, moderate muscular weakness with fatigability, unsupported gait, and balance

Table 1 Biochemical and molecular alterations in members of the reported family

Sample	Exam[a]	Reference range	Subject/age (years) (Fig. 1)				
			I-I/57	I-II/57	II-2/35	II-3/33	II-4/23
CSF	HVA	98–450 nmol/L	NP	NP	NP	124.3	169.3
	5HIAA	45–135 nmol/L	NP	NP	NP	30.3	50.4
	MHPG	28–60 nmol/L	NP	NP	NP	18.6	12.9
	3-OMD	<50 nmol/L	NP	NP	NP	521.8	328.4
	5HTP	<10 nmol/L	NP	NP	NP	65.6	64.3
Blood	VMA	26–63 nmol/L	NP	NP	28	6.2	10.2
	HVA	41–119 nmol/L	NP	NP	23	25.8	24.8
	5 HIAA	44–79 nmol/L	NP	NP	8.1	8.1	7,2
	MHPG	8–22 nmol/L	NP	NP	12.8	3.5	2,3
	Prolactin	4.80–23.30 ng/mL	NP	NP	9,9	159	145
Urine	Dopamine	65–400 μg/24 h	NP	NP	NP	1494	619
Plasma	AADC activity	18–43 nmol/L/min	6.2	7.2	3.7	Undetectable	Undetectable
DNA	*DDC* genotype		p.Tyr37Thrfs*5 (c.105delC)	p.F237S (c.710 T>C)	p.Tyr37Thrfs*5 (c.105delC)	p.Tyr37Thrfs*5 (c.105delC) p. F237S (c.710 T>C)	p.Tyr37Thrfs*5 (c.105delC) p. F237S (c.710 T>C)

[a] *AADC* aromatic L-aminoacid decarboxylase, *HVA* homovanillic acid, *5HIAA* 5-hydroxyindoleacetic acid, *3OMD* 3-*O*-methyldopa, *MHPG* 3-methoxy-4-hydroxyphenylglycol, *5HTP* 5-hydroxytryptophan, *VMA* vanillylmandelic acid, *DDC* dopa decarboxylase gene, *NP* not performed

impairment with frequent falls especially in the evening. WAIS-R IQ scored 72 (verbal IQ = 77; performance IQ = 65). Language and socialization skills were relatively preserved.

Biochemical Phenotype and Genotype

Table 1 shows the dosage of biogenic amines in blood, urine, and cerebrospinal fluid (CSF).

CSF of patients 1 and 2 were collected after an overnight fast when they were 33 and 23 years old, respectively. 5-Hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), 3-*O*-methyldopa (3OMD), and 3-methoxy-4-hydroxyphenylglycol (MHPG) were assessed in CSF by high-performance liquid chromatography (HPLC) with electrochemical detection.

The HPLC analysis of catecholamines in urine was carried out using Chromsystems 6000 Catecholamines Reagent kit (Chromsystems Instruments & Chemicals GmbH). Compounds were identified and quantified by an electrochemical detector at a potential of 400–500 mV.

For the evaluation of blood biogenic amines, plasma was quickly separated after blood drawing, stored at −80°C and subsequently shipped on dry ice to the lab. Their measurement was performed according to Hartleb et al. (2003).

AADC activity in plasma was measured essentially according to Hyland and Clayton (1992).

DDC gene was analyzed by direct sequencing of exons and intron-exon boundaries by using BDT v1.1, and the samples were run on 3130XL (Applied Biosystems, Foster City, CA).

Two novel mutations, segregating with the disease, were identified (Table 1). The first [p.Tyr37Thrfs*5 (c.105delC)] was a deleterious frame shift mutation, the second a missense mutation. To assess the pathogenic role of p.F237S (c.710T>C) transition, a bioinformatics analysis was performed (Table 2).

Figure 2 shows the possible effects of the mutation on AADC protein structure.

Treatments

Patients 1 and 2 were treated with rotigotine (6 mg/day), escitalopram (200 mg/day), and pyridoxine (300 mg/day) when 32 and 22 years old, respectively. Rotigotine treatment resulted in a significant improvement in gross motor functions in both sisters (reduction in fluctuating weakness, increase in muscular strength, and improvement in balance and gait). Motor items of Movement Disorder Society Unified Parkinson's Disease Rating scale (UPDRS-part III) assessed a prominent improvement in gait and postural

Table 2 Bioinformatics evaluation of pathogenicity of p.Phe237Ser

Software	Output	Interpretation
SIFT: http://sift.jcvi.org/	Score: 0	Amino acids with probabilities <0.05 are predicted to be deleterious
POLYPHEN2: http://genetics.bwh.harvard.edu/pph2/	Score: 1	Probably damaging with a score of 1
MUPRO: http://mupro.proteomics.ics.uci.edu/	Confidence Score: −0.5427525	Score near −1 means high confidence in decreased stability
MUTATION TASTER: http://www.mutationtaster.org/	Prob: 0.99999985746648	Prediction – disease causing: the probability value is the probability of the prediction, i.e., a value close to 1 indicates a high "security" of the prediction

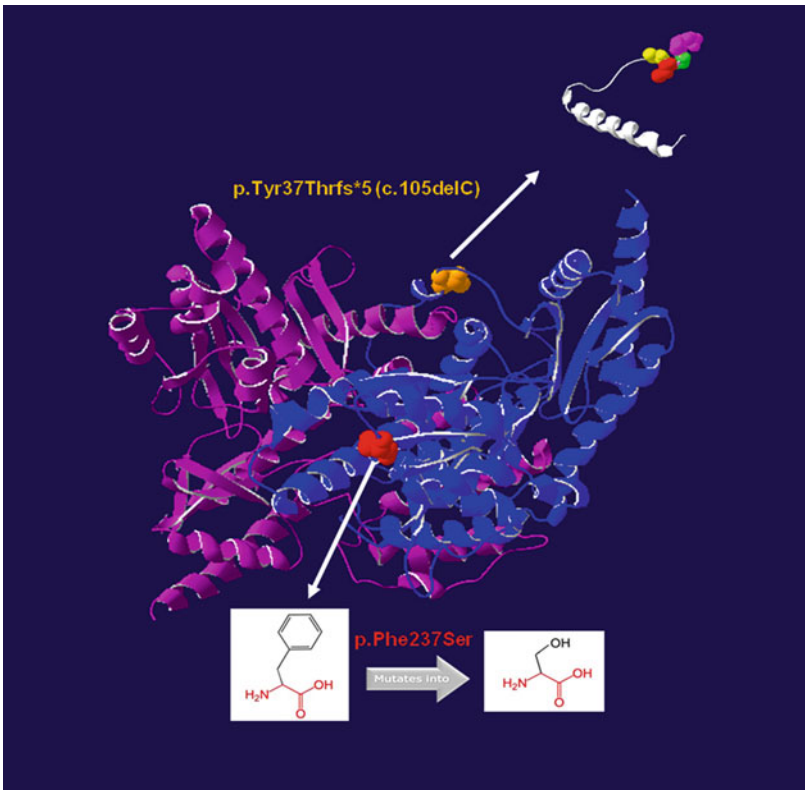

Fig. 2 The figure shows the consequences of the two mutations on the protein encoded by the gene *DDC*, as assessed by the software SwissPdbViewer version 4.1.0. The mutation c.105delC generates a premature stop codon after the change of 4 amino acids (Tyr>Thr in *yellow*, Leu>Cys in *red*, Arg>Gly in *green*, and Pro>Arg in *pink*): p.Tyr37Thrfs*5. Nevertheless, it is very likely that the stop mutation causes an early degradation of RNA by NMD (Nonsense Mediated Decay). Project HOPE (retrieved from http://www.cmbi.ru.nl/hope/home) (Venselaar et al. 2010) analysis of the mutation p.F237S suggested that : i) while the wild-type residue secondary structure, according to Uniprot, is a β-strand, the mutant residue forms a different secondary structure, which potentially destabilizes the local conformation; ii) the residue is hidden in the core of a domain that may be altered by the mutant residue; iii) the mutant residue is smaller than the wild-type residue; therefore, the mutation causes an empty space in the core of the protein; iv) the mutation would cause loss of hydrophobic interactions in the protein core

stability in patient 1 and in hand movement in patient 2. Patient 1 also became able to run slowly without falling.

Patient 1 experienced a transient recurrence of oculogyric crises. Patient 2 presented, with rotigotine at the dosage of 6 mg/day, an increase in multifocal myoclonias and in the reappearance of oculogyric crises, which required a temporary dosage reduction. A return to 6 mg/day dose, three months later, was well tolerated. In both patients, rotigotine normalized the blood prolactin levels within a few days [prolactinemia decreased from 159 to 14.8 ng/mL in patient 1 and from 145 to 12.4 ng/mL in patient 2 (reference ranges: 4.80–23.30 ng/mL)]. In both sisters, no effects were observed on orthostatic hypotension.

The heterozygote sister received rotigotine and pyridoxine with no obvious improvement.

Discussion

Even though presenting with the typical early symptoms denoting the severe forms of AADC deficiency, our patients experienced a relevant clinical stabilization and spontaneous improvement of their neurological status during adolescence and young adulthood (Pons et al. 2004; Brun et al. 2010). This clinical pattern broadens the phenotypic spectrum of AADC deficiency (Pons et al. 2004; Manegold et al. 2009; Lee et al. 2009; Brun et al. 2010).

In a larger series of AADC-deficient patients published so far, the overall mortality associated with the disease was about 10% and the majority of the remaining subjects showed a poor response to the treatment, experiencing a several neurological impairment (Brun et al. 2010). Furthermore, among the few cases with milder presentation and protracted clinical observation, the spontaneous improvements we observed in our cases as they grew older have not been reported (Pons et al. 2004; Chang et al. 2004; Tay et al. 2007; Manegold et al. 2009; Brun et al. 2010). Despite the severe clinical presentation and the undetectable plasma AADC activity (Brun et al. 2010), in our patients CSF homovanillic acid (HVA) was surprisingly within the normal range, and 5-hydroxyindoleacetic acid (5HIAA) was only marginally reduced. Therefore, the increase of 3-*O*-methyldopa and 5-hydroxytryptophan was the most relevant biochemical alteration denoting AADC defect (Table 1). We are not aware of serial assessments of biogenic amines in CSF of AADC-deficient patients. In a single case examined at the ages of 3 and 18 (Claudia Carducci, personal communication), the concentrations of HVA and 5HIAA remained relatively stable (69 and 66 nmol/L and 18 and 36 nmol/L, respectively). However, taking into account the brain requirement of biogenic amines and their age-related reference values in CSF, the gap between pathological and normal levels of HVA and 5HIAA declines with the age. Accordingly the biphasic clinical course in our patients might arise from the combined effect of a high residual enzyme activity in the brain and the decreased demand of mature brain for biogenic amines. As the blood AADC activity is concerned, it has been already reported that the enzyme activity in blood does not predict the level of biogenic amines in CSF (Hyland et al. 1992; Fiumara et al. 2002; Pons et al. 2004; Wassenberg et al. 2012). An adjunctive compensatory mechanism has been suggested by the murine model of AADC deficiency where a progressive autoregulation of dopaminergic (but not of serotoninergic) network, resulting in an increase of brain dopamine levels, developed in adulthood, as a consequence of pre- and postsynaptic adaptive mechanisms (Lee et al. 2013).

Transdermal rotigotine was extremely effective in improving gross motor functions as well as in normalizing blood prolactin in AADC defect both in these two sisters and in a previously reported 12-year-old boy (Mastrangelo et al. 2013). The transient signs of dopaminergic dysregulation, observed in the present patients, but not in the previously reported pediatric patient, could reflect the abovementioned age-related dopaminergic change leading to a possible postsynaptic hyper-recruitment of dopamine receptors (Lee et al. 2013; Mastrangelo et al. 2013). It is unclear whether sexual differences in morphology and functions of the monoaminergic system, which have been demonstrated in murine models, could also play a role (Reisert and Pilgrim 1991)[14]. Previous clinical observations suggested that women are relatively unresponsive to therapy (Pons et al. 2004). While, in general term, our experience does not support this hypothesis, the lack of affected males carrying the mutation we found makes impossible for us to contribute to this topic.

Eyelid ptosis and fluctuating muscle power in AADC-deficient patients were sometimes misinterpreted as myasthenic symptoms (Tay et al. 2007; Brun et al. 2010). The presence of the electromyographic myasthenic-like alteration in patient 1 is difficult to interpret. Presently, systematic EMG studies in patients with AADC deficiency are lacking. The well-known effects of DAP on dopamine and norepinephrine release can explain the partial improvement observed in patient 1 (Scheer and Lavoie 1991).

A mean AADC enzyme activity of 35–40% of the normal reference range has been reported in asymptomatic heterozygotes (Verbeek et al. 2007). The concurrence of a low residual AADC activity and unusual severity of cerebral palsy in the sister of the two affected patients is intriguing. It is a matter of conjecture if this was a change association or, alternatively, if AADC defect may have contributed in increasing the brain vulnerability in this patient.

Conflicting opinions exist as to the importance of early treatment for the outcome of the disease (Brun et al. 2010). The present adult diagnosed sisters were responsive to a combined pharmacologic treatment as previously reported in early diagnosed and treated patients (Hyland et al. 1992, Pons et al. 2004; Manegold et al. 2009; Brun et al. 2010). In conclusion, present cases suggest that (1) AADC defect is not a progressive neurological disease and behaves rather as a neurodevelopmental disorder that improves during the second decade of life; (2) treatment-naïve adults can still respond well to neurotransmitter therapy; and (3) the possibility of a mild presentation of AADC deficiency should be considered when examining young adults with asthenic and parkinsonian symptoms.

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Compliance with Ethics Guidelines

The work described in the manuscript has been realized in accordance with Italian law and with international ethics guidelines.

Synopsis

AADC deficiency behaves as a neurodevelopmental disorder that improves and responds to neurotransmitter therapy during the second decade of life.

Conflict of Interest

All the authors of this chapter declare that there are no conflicts of interest.

Ethics Approval

Not applicable, not required.

Patient's Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

Authors' Contribution

Vincenzo Leuzzi planned the manuscript and realized the first draft and the final revision. He directed the diagnostic and therapeutic management of the patients since the moment of the diagnosis. He serves as guarantor for the article, he accepts full responsibility for the work and/or the conduct of the study, and he has access to all the related data and controlled the decision to publish.

Mario Mastrangelo took part in the planning of the work described in the manuscript, in its conduct and reporting. He collaborated in the diagnostic and therapeutic management of the patients since the moment of the diagnosis.

Agata Polizzi took part in the reporting of the work described in the manuscript, and she was responsible for the follow-up of the patients since the early infancy.

Cristiana Artiola realized the molecular genetic analysis of DDC gene in all the members of the reported family and the related bioinformatic evaluation that is reported in Fig. 1. She also took part in the conduct and in the reporting of the work described in the manuscript.

André B.P. van Kuilenburg participated in the conduct and in the reporting of the work described in the manuscript and realized AADC enzyme activity and plasma biogenic amine measurement in all the members of the reported family.

Carla Carducci realized the molecular genetic analysis of DDC gene in all the members of the reported family and revised the bioinformatic evaluation that is reported in Fig. 1. She also took part in the conduct and in the reporting of the work described in the manuscript.

Martino Ruggieri took part in the conduct and in the reporting of the work described in the manuscript, and he collaborated in the follow-up of the patients since the early infancy.

Rita Barone took part in the conduct and in the reporting of the work described in the manuscript, and he collaborated in the follow-up of the patients since the early infancy.

Barbara Tavazzi took part in the conduct and in the reporting of the work described in the manuscript and realized biogenic amine urinary measurements in the members of the reported family.

Nico G.G.M. Abeling participated in the conduct and in the reporting of the work described in the manuscript and realized AADC enzyme activity and plasma biogenic amine measurement in all the members of the reported family.

Lida Zoetekouw participated in the conduct and in the reporting of the work described in the manuscript and realized AADC enzyme activity and plasma biogenic amine measurement in all the members of the reported family.

Vito Sofia participated in the conduct and in the reporting of the work described in the manuscript, and he collaborated in the follow-up of the patients in adult age.

Mario Zappia took part in the drafting of the manuscript, and he collaborated in the follow-up of the patients in adult age.

Claudia Carducci participated in the conduct and in the reporting of the work described in the manuscript and realized the cerebrospinal fluid measurements of biogenic amine in the two reported patients.

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