Clinical Case Report

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When dysphoria is not a primary mental state

A case report of the role of the aromatic L-aminoacid decarboxylase

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Abstract

Rationale: The aromatic L-amino acid decarboxylase (AADC) deficiency (AADCD) is a rare, autosomal recessive neurometabolic disorder caused by a deficit of the AADC that is involved in serotonin and dopamine biosynthesis, causing as a consequence, their deficits, but also a lack of norepinephrine and epinephrine, given that dopamine is their precursor.

Patient concerns: We report the case of a Caucasian 43-year-old woman heterozygous for p.Ser250Phe in *DDC*, encoding for AADC with a positive family history for behavioral problems.

Diagnoses: Since adolescence, she manifested behavioral abnormalities. Three months before the admission to our hospital, she presented with a permanent dystonic posture at the 4 limbs with numbness and tingling, diplopia, and low potassium levels. She was treated with muscle relaxants and potassium, but with no results. Olanzapine was administrated, worsening mood problems. Later, after fever, low potassium levels, and increased difficulty to move, she was admitted to the neurology unit where, after bradycardia alternating with atrial and ventricular fibrillation, she had loss of consciousness. She started to complain involuntary parossistic eye and head movements, bilateral ptosis, oculogyric crises with dystonia of the head, muscle hypotrophy, and absent deep tendon reflexes. During the hospital stay, she continued having episodes of untreatable bradycardia and fever.

Interventions: Hemocultures were performed, resulting positive for *Enterococcus faecalis* and *Acinetobacter baumanii*. Whole exome sequencing was performed evidencing that the patient harbored the heterozygous p.Ser250Phe variant in the gene *DDC*.

Outcomes: A treatment with Pyridoxine and Pramipexole was prescribed, but never started because she died.

Lessons: The heterozygosity for p.Ser250Phe may have influenced the clinical manifestations, given that the patient presented some overlapping symptoms with those in AADCD, but while AADCD normally is diagnosed during childhood, the fact that the patient carried the mutation in heterozygosity may have alleviated and delayed the clinical manifestations.

Abbreviations: 5HT2 = serotonin type 2, AADC = aromatic L-amino acid decarboxylase, AADCD = aromatic L-amino acid decarboxylase deficiency, EEG = electroencephalography, MAO = monoamine oxidases, MRI = magnetic resonance imaging.

Keywords: aromatic L-amino acid decarboxylase, dopamine, exome sequencing

1. Introduction

The aromatic L-amino acid decarboxylase deficiency (AADCD) is a rare, autosomal recessive neurometabolic disorder, due to a deficit of the Aromatic L-amino acid decarboxylase (AADC), which is the final enzyme in serotonin and dopamine biosynthesis and it is consequently involved in norepinephrine and epinephrine production, since dopamine is the precursor for both.[1]

The global incidence of AADCD is unknown, but it seems to be more prevalent in the Asian populations, probably due to a founder effect.[2]

Symptom onset is variable, even though, in patients carrying homozygous mutations, they typically occur during the first months of life.[3]

The phenotypic spectrum of AADCD is broad and can range from very severe to relatively mild. Key symptoms of AADCD are: axial hypotonia (sometimes associated to limb hypertonia), movement disorders (ie, oculogyric crises, dystonia, and hypokinesia), developmental delay, and autonomic symptoms (ie, diarrhea, episodic hypoglycemia, nasal congestion, ptosis, bradycardia, excessive sweating, hypotension, or orthostatic hypotension); and all key symptoms ranged in severity from mild to very severe. Rarely, AADCD may manifest also with epileptic seizures and/or sleep disturbances (insomnia, hypersomnia, and severe sleep apnea).[4] Behavioral problems, such as irritability, excessive crying, dysphoria, can be a great burden for patients and caregivers but are not well defined in the literature.[3,4] There are no specific pattern related to deep tendon reflexes (which can be decreased, normal, or increased)

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or pathological reflexes, including Babinski sign, which have been sometimes reported.[4] Additional clinical findings may include gastrointestinal problems, like diarrhea, constipation, gastroesophageal reflux, and feeding difficulties with difficulties in gaining weight and failure to thrive, which may require a gastrostomy.[4] Even though hormone deficiencies have never been demonstrated as part of AADCD, increased prolactin levels may be found, since dopamine is an inhibitor of prolactin secretion.[5]

There is no specific magnetic resonance imaging (MRI) AADCD pattern, thus, since brain imaging may be normal or may disclose cerebral and cortical atrophy,[3,4] leukomalacia,[2] degenerative changes of white matter, thinning of corpus callosum, prominent ventricular bodies, leukodystrophy-like patterns, and hypomyelination.[3] Consequently, routine brain images may be useful for differential diagnosis. Even the electroencephalographic pattern is not specific, ranging from normal to epileptiform abnormalities with unspecific pattern.[4] Thus being useful for differential diagnosis between oculogyric crises and epileptic events.

Due to the rarity of AADCD, there is limited international clinical expertise for evidence-based management. Moreover, treatment response and strategies are variable and in most cases, cannot be predicted.[3] First line treatment agents are selective dopamine agonists, monoamine oxidases (MAO)-inhibitors, and pyridoxine. However, combining multiple drugs that is symptomatic medications like anticholinergic agents, melatonin, benzodiazepines, and alpha-adrenoreceptor blockers, should be considered, possibly applying a step-wise, continuous and gradually increasing doses.

Herein, we report a Caucasian 43-year-old woman with symptoms overlapping to those of AADCD, lately recognized, with a bad outcome. Early AADCD diagnosis is essential for patients and family members in order to manage with a multidisciplinary approach to the disease.

2. Case report

The patient is a 43-year-old woman, second child from non-consanguineous parents, born from normal delivery. Family history was positive for sudden death, and behavioral problems (Fig. 1). She was firstly evaluated in the intensive care unit of our research institute, coming from the emergency of another hospital with the suspected diagnosis of drug or alcohol abuse induced encephalopathy. History was positive for cognitive and behavioral problems, with abnormal thinking, personality changes, poor concentration, confusion, memory impairment, anxiety, poor judgment, on carbolithium treatment. Three months before admission, her brother referred an acute onset of permanent dystonic posture at the 4 limbs with numbness and tingling, diplopia, and low potassium levels, with no consciousness alterations, being able to talk and to report her symptoms. Thus, she was admitted to a neurology unit and treated with muscle relaxants and potassium. After a few days, she presented with neurological bladder and she was catheterized. Even though the dystonic posture was still present, patient was discharged and, considering the psychosis worsening, treatment with carbolithium was switched to olanzapine. This choice was made because olanzapine, a well known antipsychotic agent, exhibits regional mesolimbic dopaminergic selectivity and a broad-based pharmacology encompassing serotonin, dopamine, muscarinic, and adrenergic receptor binding affinities, making olanzapine the first line neuroleptic drug for psychotic disorders. One month after discharge, she began to complain of difficulty in walking and she was confined to bed, until the formation of a sacral decubitus, followed by fever, increased difficulty in movements and low potassium levels. Then, she was again admitted to the neurology unit where she presented a marked bradycardia alternating with atrial and ventricular fibrillation episodes. Following an episode of cardiac arrhythmias, she lost consciousness, needing orotracheal intubation and she was transferred to the intensive care unit of our Institute. On admission, she started to complain involuntary parossistic eye and head movements, bilateral ptosis, oculogyric crises with dystonia of the head, generalized muscle hypotrophy, absent deep tendon reflexes, with no pathological reflexes. Hemocromocytometric test, biochemical parameters, and urine analysis resulted in normal range. Deeply investigating her history, the patient, at the age of 16 year-old, firstly started to complain of behavioral abnormalities, with depressed mood alternated with dysphoria and easy irritability. Her brother referred a difficulty to gain weight, sleep disorders with insomnia, increased prolactin levels and some episodes of bradycardia, hypotension and hypoglycemia. Moreover, a sister died for sudden death and the patient's children having the same behavioral problems (the female 1 was on Carbolithium) (Fig. 1). During the hospital stay, electroencephalography (EEG) was performed, showing a diffuse theta mixed to paroxysmal activities. Brain MRI shows symmetric hyperintense lesions with restricted diffusion confined to the globus pallidus (Fig. 2A, B). During the hospital stay in the intensive care unit, she continued to manifest episodes of untreatable bradycardia and fever. Blood tests were unremarkable, with a white blood count within 12,000 cells/μL for a few days. Then, she began to present a pancytopenia and a procalcitonin increase (from 1.2 to 6.4 ng/mL), so that hemocultures were performed. They resulted to be positive for *Enterococcus faecalis* and *Acinetobacter baumanii* and as a consequence the antibiotics tigecycline and colistin were infused. Because of such clinical picture, and considering the progressive worsening of her clinical conditions, with marked bradycardia alternating with atrial fibrillation, she needed sedation. In order to achieve a proper diagnosis, we decided to perform a whole exome sequencing with the informed consent of the legal guardian (patient's brother), according to Illumina protocols on a MiSeq instrument (Illumina San Diego, CA), revealing different mutations including p.Ser250Phe (c.749C>T, rs137853208) in the *DDC* gene, harbored in heterozygous state (Table 1). The diagnosis of AADCD was made and treatment with pyridoxine (vit B6) at the dosage of 200 mg/d, and Pramipexole at the dosage of 0.005 mg/kg/d was then prescribed, but never started because she suddenly died.

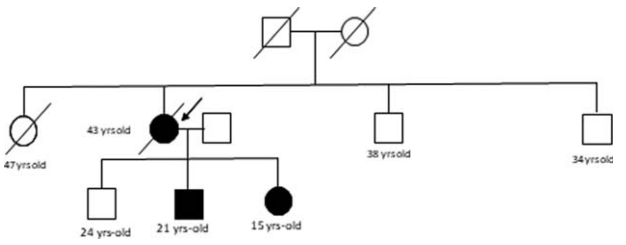

Figure 1. Family tree. The arrow indicates the patient evaluated in this clinical case. Black circles and square indicate an early onset of psychiatric manifestations. Deaths are indicated with the oblique lines.

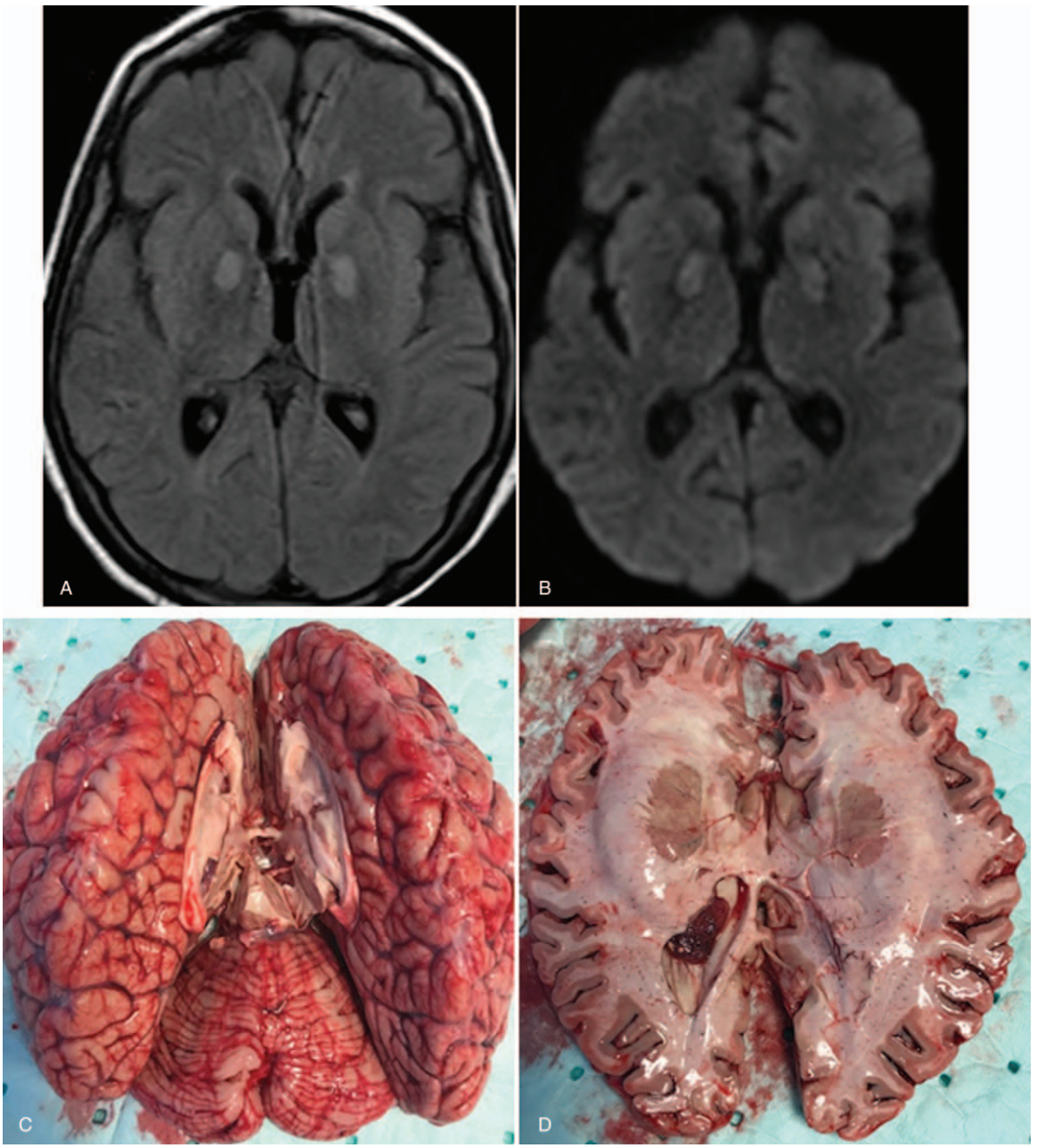

Figure 2. A, Axial FLAIR image, (B) axial DWI image. Symmetric hyperintense foci on FLAIR sequence with restricted diffusion in the globus pallidus. C and D, Macroscopic images of the brain, showing the absence of inflammatory process.

Considering the peculiar clinical picture and the abundant milk secretion after death, to confirm diagnosis, an autopsy was done, showing a condition of sepsis with no macro- and microscopic brain abnormalities (Fig. 2 C, D). A timeline with the main events of patient's history is showed in Figure 3.

3. Discussion

Herein, we report on a Caucasian 43-year-old woman, harboring the p.Ser250Phe in the *DDC* gene in heterozygous state, presenting with a psychiatric onset phenotype, in which the use of olanzapine may have contributed to worsen the clinical picture.

AADCD is an early onset rare genetic disorder, causing a combined deficiency of serotonin, dopamine, norepinephrine and

Table 1

Mutations detected at the next generation sequencing analysis, according to the database clinical variant.

Gene	Mutations
DDC	p.Ser250Phe, c.749C > T, rs137853208 (heterozygous state)
ABCC6	p.Val614Ala, c.1841T > C, rs12931472 (heterozygous state)
KLKB1	p.Ser143Asn, c.428G > A, rs3733402 (heterozygous state)
BCHE	p.Gly143Asp, c.428G > A, rs201820739 (heterozygous state)
PRLR	p.Ile170Leu, c.508A > C, rs72478580 (heterozygous state)
ASAH1	p.Thr58Met, c.173C > T, rs145873635 (heterozygous state)
STOX1	p.Glu608Asp, c.1824A > C, rs10509305 (heterozygous state)
ABCC6	p.His632Gln, c.1896C > A, rs8058694 (homozygous state)
ABCC6	c.1338 + 7C > G, rs9940089 (homozygous state)

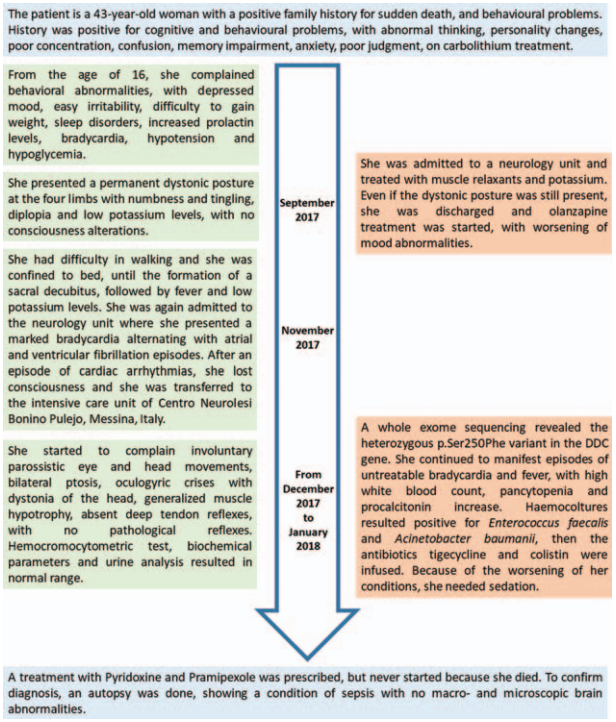

Figure 3. Timeline showing the patient's history.

epinephrine. Key clinical symptoms are hypotonia, movement disorders (especially oculogyric crisis, dystonia, and hypokinesia), developmental delay, and autonomic symptoms. Clinical phenotype is widely variable, with no clear genotype/ phenotype correlation. The clinical onset of our patient was with behavioral symptoms, treated with olanzapine. Since the olanzapine administration, the patient clinical picture rapidly worsened. This aspect could be explained by the intrinsic mechanism of action of olanzapine, which block dopamine and serotonin production through a combination of dopamine and serotonin type 2 (5HT2) antagonism.[6] Such effect, in combination with the dopamine and serotonin depletion induced by the AADC may have determined the clinical picture. Another element supporting such aspect was the presence of abundant milk secretion after death, even reported in the dead sister. Such phenomenon may be explained by the role of dopamine in the regulation of prolactin secretion. In fact, dopamine inhibits the basally high-secretory tone of the cell, through a direct effect on the anterior pituitary lactotrophs, by binding to D2 receptors expressed on the cell membrane of the lactotroph, that reduce prolactin exocytosis and gene expression by a variety of intracellular signaling mechanisms.[7]

To date, most of the reported AADCD patients are Asian, possibly due to the founder variant IVS6+4A>T[2]; the reported Caucasian cases are 33 all over the world.[4]

Our patient harbored the p.Ser250Phe in the *DDC* gene, which is reported to be one of the most frequent mutations causing the AADCD. Serine at position 250 is not essential for the catalytic activity of this enzyme; however, the mutation to Phenylalanine caused about a 7-fold decrease of its catalytic activity. It was suggested that the mutation did not involve the intracellular mRNA levels, but it seems that it caused a faster degradation compared to the wild-type, through the proteasome.[8] The enzyme activity in deficient patients was reported to be decreased compared to controls. Instead, heterozygotes presented intermediate levels of enzyme activity, with a mean percentage residual activity level of the enzyme of about 35% to 40%,[9] but this residual activity seems sufficient and was not associated with clinical signs and symptoms. However, a study reported an increased rate of psychiatric disease in 2 families.[10] In a case report, Leuzzi et al[11] reported a case of 2 sisters diagnosed during adulthood, while another heterozygous sister was born after a complicated twin pregnancy and diagnosed as affected by cerebral palsy and intellectual disability. It is intriguing if the presence of the AADC defect in this sister may have worsened her condition, increasing brain vulnerability. The heterozygosity for the p.Ser250Phe mutation may have influenced the clinical phenotype in our patient. Indeed, the patient clinical manifestations presented some overlapping symptoms with those in AADCD. However, AADCD normally is clinically evident during childhood, but the fact that the patient harbored the mutation in heterozygosity may have alleviated and procrastinated the clinical manifestations.

In our patient, the AADCD onset was with behavioral abnormalities. Early recognition of such clinical condition, especially when the onset is just psychiatric, is important in order to prevent possible complications related to disease progression. Moreover, there should be awareness for possible cardiac complications in AADCD patients during potentially stressful situations and cardiac monitoring during these events is recommended. Indeed, a prompt AADCD diagnosis is essential to screen other family members, especially for those who present with early onset psychiatric manifestations. Finally, once the diagnosis is achieved, a multidisciplinary team, including physiatrist, cardiologist, neurologist and paramedical therapy services, is essential in the care for such AADCD patients, and a psychological support should be given to patient and caregivers.

Author contributions

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