Oromandibular Dystonia is a Prominent Feature in Patients with Aromatic L-Amino Acid Decarboxylase (AADC) Deficiency

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Abstract

Aromatic L-Amino acid decarboxylase (AADC) deficiency is a rare neurometabolic disorder due to a homozygous or compound heterozygous pathogenic variant of the DDC gene, resulting in low synthesis of the biogenic amines dopamine, serotonin, epinephrine, and norepinephrine. Most patients had severe expression of the disease with global developmental delay, early hypotonia, movement disorders such as oculogyric crises, tremor, and dystonia. Oromandibular dystonia (OMD) is rarely recognized in patients with AADC deficiency. The aim of this study was to describe OMD in detail in 4 patients with AADC deficiency. OMD occurred in isolated form or in association with oculogyric crises, increasing the difficulty in care patients during the crises. The main form of OMD was tongue dystonia associated with mouth opening dystonia. AADC deficiency must be included in the list of genetic causes of OMD.

Keywords

Aromatic L-amino acid decarboxylase deficiency, DDC gene, Oculogyric crises, Oromandibular dystonia.

Introduction

Aromatic L-amino acid decarboxylase (AADC) deficiency (OMIM 608643) is a rare recessive neurometabolic disorder due to a defect in the synthesis of neurotransmitters in the brain [1]. AADC deficiency results in partial or complete blockade of the synthesis of the biogenic amines dopamine, serotonin, epinephrine, and norepinephrine. The disease is caused by homozygous or compound heterozygous pathogenic variants in the dopa decarboxylase (DDC) gene [2].

Since the initial description in 1990 [3], several articles have been published with patient series, and the number of studies has increased as knowledge and technical capabilities to study defects in neurotransmitter synthesis have expanded. A review study published in 2022 analyzed data from 261 documented cases [4].

Although the worldwide incidence of AADC deficiency is not known, a pilot study in Taiwan using newborn screening found a prevalence of 1:32,000 [5]. The disease is more prevalent in the Asian population, likely due to a founder effect of a specific mutation [2]. In addition, preliminary results from newborn screening studies in central Europe confirmed the former estimated prevalence of 1–2 in around 500.000 newborns [6]. However, in an at-risk population of children with suggestive symptoms of neurotransmitter dysfunction, in whom other pathologies were excluded, and whose samples were screened for neurotransmitter disorders in a reference laboratory, the prevalence was 1:900 [7].

The clinical presentation of AADC deficiency includes signs and symptoms directly related to the defect in synthesis of the involved neurotransmitters. Most patients present with severe motor developmental delay associated with axial hypotonia. The first symptoms usually appear between 2 and 5 months of age [2]. Movement disorders usually appear early, especially dystonia and hypokinesia, but tremor, chorea, and athetosis have also been

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described [2,4]. Oculogyric crisis (OGC), commonly observed in AADC deficiency and other neurotransmitter disorders, are a manifestation of dystonia of the extrinsic eye muscles that can last from minutes to hours [2,4,8]. Autonomic symptoms such as eyelid ptosis, stuffy nose, chronic diarrhea, excessive sweating, hypersalivation, fluctuations in blood pressure and heart rate are due to low levels of epinephrine and norepinephrine [8,9]. Temperature instability, mood and behavioral problems, and sleep disturbances are also common in patients with AADC deficiency [2]. Due to the role of catecholamines in regulating blood glucose levels, cases of hypoglycemia have been reported, especially during the neonatal and infantile period [10]. Data from the International Working Group on Neurotransmitter related Disorders showed the presence of development delay and truncal hypotonia as the most common initial symptom of AADC deficiency. Additionally, thermoregulation disorders and OGC were more prominent than in others neurotransmitter disorders. New insight also revealed an increase in the rate of premature births in AADC deficiency populations [11].

Oromandibular dystonia (OMD) is a specific form of dystonia characterized by involuntary, repetitive, and persistent movements of the lower face, jaw, tongue, and pharynx. The estimated prevalence of OMD is 6.9 cases/100,000, with a female predominance (2:1) [12]. Most cases of OMD occur in combination with blepharospasm (Meige syndrome) or in association with dystonia in other parts of the body, occurring in isolation in only 2-23% of cases [13]. The list of etiologies of OMD is extensive, the most common being primary or idiopathic forms of dystonia, drug-induced dystonia, associated with facial trauma, after anoxia states, head trauma, and neurodegenerative diseases [14]. Some of the genetic causes of OMD are neurotransmitter disorders related to dopamine metabolism, such as dopa-responsive dystonia (GTP-CH1) and dopamine transporter deficiency syndrome [14]. AADC deficiency is another neurotransmitter disorder in which dopamine dysfunction is a hallmark of the disease. However, there are limited data on OMD in patients with AADC deficiency. The aim of this article is to describe the phenomenological features of OMD in a series of patients with AADC deficiency.

Methods

The study was approved by the local ethics committee, and informed consent was obtained from those responsible for enrollment in the study. In the included patients, the diagnosis of AADC deficiency was suspected by clinical symptoms and 3-O-methyldopa (3-OMD) measurement, and confirmed by enzyme measurement, and molecular analysis. We analyzed videos obtained with family consent to examine clinical manifestations and movement disorders. For a second evaluation of the clinical characterization of OMD, the videos were also analyzed by a neurologist specialized in movement disorders. Therefore, we selected 8 videos from 4 patients with AADC deficiency whose analysis confirmed the diagnosis of OMD. The videos were analyzed in detail in terms of clinical phenomenology for classification of OMD.

Results

We described 4 patients with a confirmed diagnosis of AADC deficiency who presented with OMD as a prominent and persistent symptom. Table 1 shows the demographic data of the 4 patients.

Table 1. Demographic data and main test results.

	Age	Sex	Age at diagnosis	Brain MRI	EEG	AADC activity (36-129 Nmol/l/min)	DDC variant	Treatment and response
Patient 1	22 y	Male	17 y	Normal	Focal epileptiform discharge	0,0	c.1040G>A p.(Arg347Gln) Pathogenic + c.564_568dup p.(Gln190Profs*13) Pathogenic	Piridoxine, melatonin: improvement of sleep and lower frequency of paroxysmal events
Patient 2	2 y 3 mo	Female	18 mo	Normal	Normal	<0,22	c.1040G>A (p.Arg347Gln) Homozygozis Pathogenic	Piridoxin, melatonin, pramiprexol: no significant improvement
Patient 3	6 y	Female	4 y	Normal	Normal	0,69	c.330_334dup p.(Gln112fs*13) Likely Pathogenic + c.1040G>A p.(Arg347Gln) Pathogenic	Pyridoxol-phospate, selegilin, pramiprexol: lower frequency of paroxysmal events
Patient 4	12 y	Male	2 y 8 mo	Normal	Normal	0,91	c.1040G>A p.(Arg347Gln) Homozygozis Pathogenic	Pyridoxol-phospate, selegilin, pramiprexol: lower frequency of paroxysmal events

Mo: months

Patient 1

A 22-year-old man, the only son of nonrelated parents, who was definitively diagnosed with AADC deficiency at the age of 17 years old. He had severe hypoglycemia during the neonatal period and chronic diarrhea during his first years of life. Despite normal clinical investigations, diarrhea was attenuated after withdrawal of gluten and lactose, and use of probiotics and symptomatic constipating medication. At 4 months of age, he showed OGC every 3 to 4 days, which were accompanied by irritability and dystonia and lasted 7 to 8 hours. After symptomatic treatment, the frequency of events decreased to every 5 days and lasted up to 5 hours. This pattern has remained stable over the years, with few fluctuations. From the first year of life, OGC was always associated with tongue movements and mouth opening (Figure 1a, Supplementary Video 1). However, he also had episodes in which the prominent feature was orolingual movement, with no eye deviation, accompanied by autonomic symptoms and lasting for hours. During his first 15 years of life, he received several anti-seizure medications without any change in his clinical picture. Despite the severity of his clinical condition, he is still able to eat orally with assistance. He has global developmental delay and cannot control his head. Neurological examination shows double hemiplegia, appendicular dystonia, joint deformities, global hypoactive tendon reflexes, kyphoscoliosis, bilateral eyelid ptosis. However, he has good eye contact and a social smile.

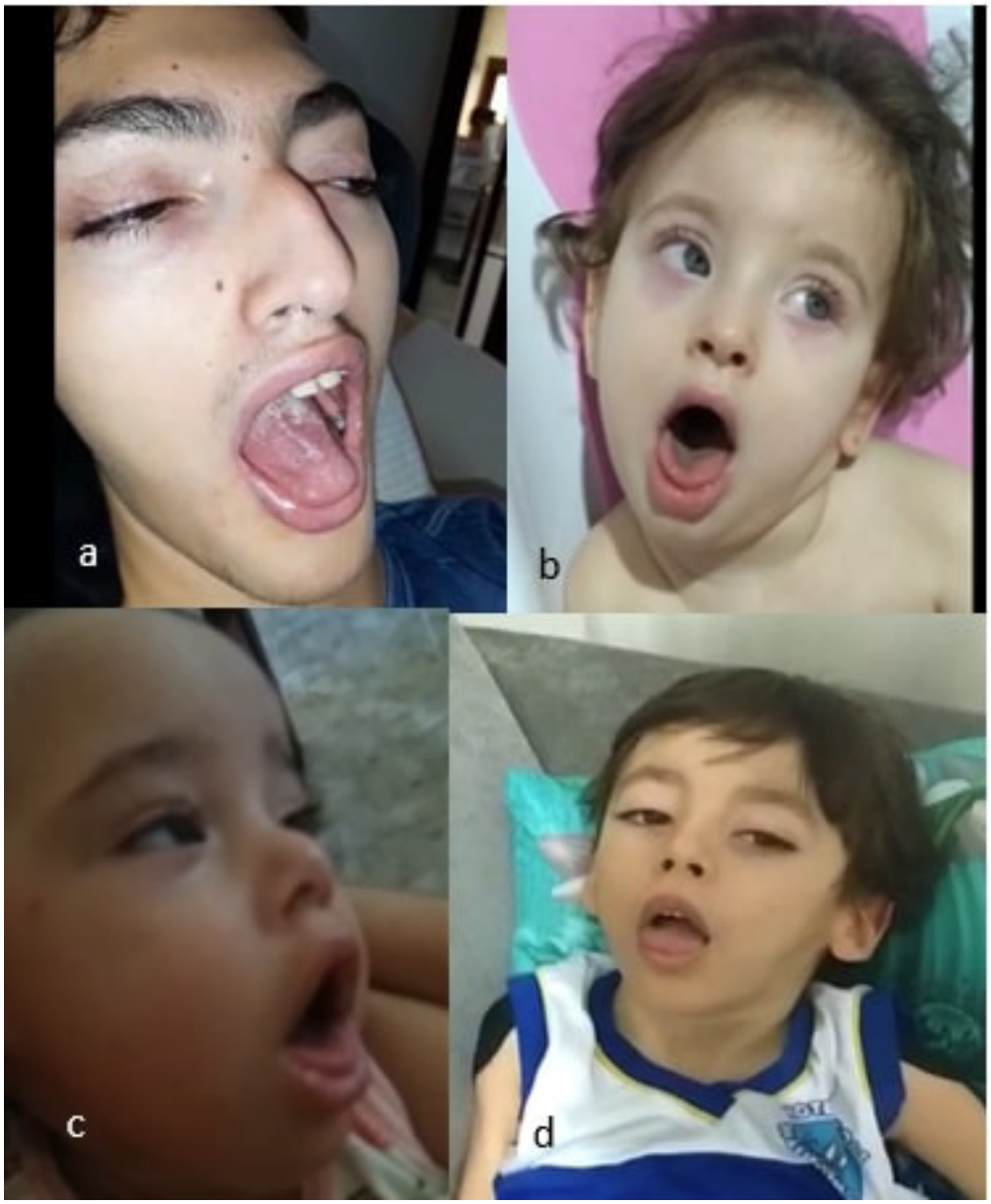

Figure 1. Photos of the 4 patients during oromandibular dystonia.

The clinical characterization of patient 1's OMD was jaw opening dystonia associated with lingua dystonia at rest and on protrusion with dystonic tremor.

Patient 2

Female, 2 years, and 3 months old, only child of a consanguineous parent diagnosed with AADC deficiency at 18 months of age. At birth, she had difficulty sucking and was unable to breastfeed. At 3 months, motor delay and hypotonia were noted. At 4-5 months of age, she experienced OGC, which was always initiated by a cry followed by an upward eye movement that lasted between 6 and 15 hours. During this time, she had bilateral ptosis of the eyelids, sweating, and disordered movements of the tongue and opening and closing of the mouth, which made oral feeding impossible. The current periodicity of the crises was 4 to 5 days.

She has no motor development, no head support, but she has good eye contact and social smile and interacts with the environment through eye contact and emotions. She has chronic nasal congestion. Neurological examination shows axial hypotonia and appendicular dystonia, mild bilateral palpebral ptosis, reduced spontaneous movements, and normal tendon reflexes.

We analyzed 3 videos of patient 2, all with similar features: predominant oscillatory rhythmic movements of alternating anteriorization and exteriorization of the tongue, although often inconstant (lingua dystonic tremor), combined with an intermittent jaw opening dystonia (Figure 1b, supplementary videos 2, 3 and 4).

Patient 3

A 6-year-old girl, the only child of nonrelated parents, who was definitively diagnosed with AADC deficiency at the age of 4 years. Oligohydramnios was observed during pregnancy, and she was born with low weight and remained in the intensive care unit with tube feeding. At the time of discharge, she was able to breastfeed. She developed with a global delay of milestones, with no head control. During the first year of life, she had recurrent aspiration pneumonia, which led to gastrostomy at 12 months of age. Oculogyric crises began at 3 months of age with preferential upward deviation, severe stiffness, profuse sweating, and sialorrhea lasting between 8 and 10 hours. During the events, she made many movements with her mouth and tongue (Figure 1c, Supplementary video 5).

She has bilateral eyelid ptosis, nasal congestion, and profuse sweating. She can interact with eye contact and social smiles. Until 12 months of age, she was treated for epilepsy and was taking several medications for seizures. On neurologic examination, she showed axial hypotonia, no head support, reduced spontaneous movements, double hemiparesis, appendicular dystonia, and normal tendon reflexes.

The characterization of OMD in patient 3 was characterized by and anteriorization and exteriorization movements of the tongue (lingual dystonic tremor). These movements were accompanied by intermittent jaw opening dystonia.

Patient 4

A 12-year-old male child was diagnosed with AADC deficiency at 2 years and 8 months of age. He was born preterm at 33 weeks' gestation and remained in the intensive care unit because of his weight gain. He had hypoglycemia and jaundice and required phototherapy for 7 days. At 4 months, delayed motor development and hypotonia were noted. At 6 months of age, OGC occurred with upward deviation of the eye lasting up to 12 hours. Initially, the crises occurred in isolation, but over time it began to be accompanied by sweating, sialorrhea, and appendicular dystonia. Later, the episodes began to include tongue and mouth movements. The frequency of events in the first years of life was daily, but with symptomatic treatment the regular frequency passed for every 7 days. He showed axial hypotonia, partial support of the head, bilateral appendicular dystonia, joint deformities, ptosis of the eyelids, and normal tendon reflexes.

We analyzed 3 videos from this patient (Figure 1d, supplementary videos 6,7 and 8). In videos 6 and 7, the predominant movement was lingual dystonic tremor, with inward and outward movements (video 6) and probable associated choreic movements (video 7). In video 8, the main feature was jaw opening dystonia.

Discussion

AADC deficiency is a rare neurometabolic disorder that may be underdiagnosed because of its similarity to other more common disorders such as cerebral palsy and epilepsy. However, an increasing number of cases have been reported in recent years. The possibility of effective treatment through gene therapy has increased suspicion of earlier diagnosis. In addition to autonomic dysfunction and global developmental delay, movement disorders are among the characteristic symptoms of AADC deficiency, specially hypokinesia, dystonia (mainly OGC), and tremor. OMD is a specific form of dystonia that can occur in patients with primary or secondary dystonia. The list of secondary causes is long, but in childhood, the dyskinetic form of cerebral palsy is a common etiology [15]. OMD secondary to drug use or as a result of infectious diseases, autoimmune encephalitis, and genetic causes of dystonia are also commonly observed in childhood [14]. Neurotransmitter disorders, especially those related to monoaminergic metabolism, often have dystonia as a characteristic clinical presentation. Movement disorders such as dystonia are one of the symptomatic pillars of AADC deficiency, the most common cause of neurotransmitter disorders [16]. However, there is a lack of studies that have analyzed in detail in terms of types of dystonia, clinical characterization, and association with other movement disorders.

The 2017 consensus guideline produced by an international working group on neurotransmitter disorders and related diseases mentions dystonia as the second most common movement disorder but does not characterize this group of symptoms in detail [2]. A systematic review also highlighted dystonia as a common symptom in AADC deficiency but did not mention OMD or other types of dystonia in the description [4]. The 2021 Italian consensus also does not mention OMD as part of dystonia in the patients described [9].

Furthermore, in a series of 63 patients, the authors described in detail the OGC and emphasized that in 76% of the cases there was an association with trunk or limb dystonia, but they did not mention OMD as one of these associated movement disorders [8].

In our small series, in addition to the OGC, OMD was a prominent finding, occurring early and persistently, in association with OGC or in isolation. In patients 1 and 2, OMD occurred in association with or without OGC, in the presence of other disease features such as autonomic disturbances that lasted for hours. These findings indicate that OMD is a common finding in patients with AADC deficiency and that it should be thoroughly investigated in these patients. As in the 4 patients described, OMD is a movement disorder that affects the quality of life of patients and their families, because all patients were unable to feed orally during the movement disorder (only 1 of the patients was tube fed) and may have been unable to consume food and water for hours.

OMD can be categorized according to clinical presentation. In a study of clinical analysis of 240 patients with OMD, the authors indicated that oromandibular mouth-opening dystonia was the most common (62.1%), followed by tongue dystonia (26.7%) and mouth-closing dystonia (20%). Mixed forms accounted for 17.9% of cases [13]. Other studies also indicate that mouth opening dystonia and mouth closing dystonia are the most common [12,14]. However, in our series of 4 cases, tongue dystonia (or lingual dystonic tremor) was the most common form, occurring in all patients. Patients 1, 2 and 3 had tongue dystonia in association with mouth opening dystonia. Patient 4 had both forms of OMD. It is worth noting that most review articles on OMD analyzed adult patients with different etiologies.

Another finding described in our patients was the occurrence of OMD associated or not with OGC. We consider this finding to be very relevant because in other series there is no detailed description of OMD, because the focus was the description of OGC. In our series, we have shown that patients with AADC deficiency can present OMD in association with or without OGC, when the patients are able to maintain good visual contact. Appendicular dystonia is often associated with OMD, as are autonomic symptoms.

Other diseases affecting dopaminergic metabolism in the central nervous system may run with OMD, but there are few reports. OMD may occur secondary to guanosine triphosphate cyclohydrolase I (GTPCH1) deficiency in rare cases of dopa-responsive dystonia [17,18,19]. In a case series of patients with dopamine transporter deficiency, the authors described OMD in 2 cases [20]. As shown in our study, AADC deficiency should also be included among the genetic etiologies of OMD.

Conclusion

OMD is a prominent finding in patients with AADC deficiency and occurs in association with OGC, but also in isolated form or in association with autonomic symptoms and appendicular dystonia. Tongue dystonia, isolated or in association with mouth-opening dystonia, is the most common clinical form of OMD in these patients. The presence of OMD is a factor that affects the quality of life of patients with AADC deficiency.

AADC deficiency should be included in the differential diagnosis of OMD in children.

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Declaration of Conflicting Interests

The authors declare no potential conflict of interests with respect to research, authorship, and/or publication of this article.

Supplementary Material

The following online material is available for this article:

Video 1
Video 2
Video 3
Video 4
Video 5
Video 6
Video 7
Video 8

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