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Novel presentation of AADC deficiency as a mild phenotype with exercise-induced dystonic crises: A case report

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ABSTRACT

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare autosomal recessive neurometabolic disorder caused by biallelic pathogenic variants in the *DDC* gene; approximately 140 patients have been described worldwide. AADC deficiency is characterised by a combined deficiency of dopamine, serotonin, adrenaline and noradrenaline causing a highly variable phenotype with developmental delay, early-onset hypotonia, movement disorders and autonomic symptoms. We expand the phenotype of this neurometabolic disorder by reporting on a paediatric patient with a mild phenotype with atypical exercise-induced dystonic crises, a feature that has not been described in AADC deficiency up till now. Additionally, we also present a second patient with typical characteristics and a severe phenotype. The diagnosis in both patients was confirmed by the presence of a homozygous pathogenic variant in the *DDC* gene and reduced AADC enzyme plasma activity. The use of whole exome sequencing-based strategies has played a crucial role in diagnosing these two patients.

1. Introduction

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare autosomal recessive neurometabolic disorder caused by biallelic variants in the *DDC* gene. The AADC enzyme is responsible for the biosynthesis of the monoamine neurotransmitters serotonin and dopamine, the latter being a precursor of adrenaline and noradrenaline. Deprivation of the AADC enzyme leads to a severe combined deficiency of these neurotransmitters [1]. Approximately 140 patients have been described worldwide since the first reported case in 1990 [2]. The most characteristic features of AADC deficiency are hypotonia (95 %) and oculogyric crises (86 %), often accompanied by hypertonia (mainly affecting the limbs), developmental delay, movement disorders (e.g. dystonia) and autonomic symptoms (e.g. temperature instability, nasal congestion) [3]. Most patients present during the first months of life, however milder cases with later onset have been described [1].

We present two paediatric cases with AADC deficiency and novel homozygous pathogenic variants in the *DDC* gene. The first case shows a typical, severe phenotype, while the second patient presents with an atypical, mild phenotype. Moreover, this is the first report of a patient with exercise-induced dystonic crises in this disorder.

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2. Case series

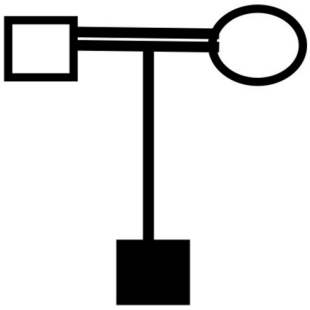
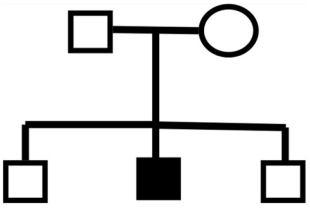
2.1. Case 1

The first patient is a three year old boy of Afghan origin. He is the first child of consanguineous parents; with uncomplicated pregnancy and birth. He first presented at the age of four and a half months with a suspicion of status epilepticus. Clinical examination showed intermittent stridulous breathing, a severe motor developmental delay (estimated developmental age of one month) with pronounced hypotonia and head lag, intermittent circular movements of both hands and frequent hyperextension of the spine and limbs. An electroencephalogram (EEG), cerebrospinal fluid examination for infectious causes, metabolic investigations and brain MRI revealed no abnormalities. Subsequently, a neurotransmitter disorder was suspected which prompted genetic investigations. A chromosomal microarray was normal. Trio whole exome sequencing (WES) with filtering for variants in a cerebral palsy (CP) gene panel, containing around 200 genes related to CP (mimics), demonstrated the presence of a homozygous c.170T > G p. (Ile57Ser) variant in the *DDC* gene (NM_001082971.2) (supplement 1). This variant had not been described in the literature, but was absent from control databases (GnomAD, ESP) and the majority of *in silico* prediction programs predicted it to be pathogenic. Cerebrospinal fluid levels of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA), two end products of the AADC metabolic pathway, were decreased. Furthermore, the plasma AADC enzyme activity was strongly reduced. These findings corroborated the genetic diagnosis of AADC deficiency. A summary of the patient's clinical and genetic data can be found in Table 1.

Following the therapeutic guidelines, treatment with pyridoxine was initiated, supplemented with increasing dosage of pramipexole shortly after [1]. Because of side effects (nausea and vomiting) and insufficient therapeutic effect, pramipexole was replaced by trihexyphenidyl. After initial mild positive effect, the dystonia worsened with more dystonic crises and teeth grinding. Selegiline was added, with slight improvement of the dystonic crises. The boy was treated with melatonin, eventually in combination with hydroxyzine, for sleeping problems. A gastrostomy was placed because of feeding difficulties and he underwent a supraglottoplasty due to laryngopharyngomalacia.

The patient is now three years old and shows severe developmental delay, dystonia, feeding difficulties and respiratory issues due

Table 1
Summary of genetic, laboratory and clinical findings.

	CASE 1	CASE 2
AFFECTED GENE	*DDC*	*DDC*
PATHOGENIC VARIANT	c.170T > G (p.Ile57Ser) (HOM)	c.941T > C (p.Met314Thr) (HOM)
SEX	Male	Male
FAMILY TREE		
AGE AT PRESENTATION	4.5 m	6y 4 m
AGE AT DIAGNOSIS	7 m	13y
DEVELOPMENTAL DELAY	Severe developmental delay	Mild intellectual disability
NEUROLOGICAL FINDINGS	Axial hypotonia Limb hypertonia Dystonia	Dystonia (exercise-induced) Oculogyric crises
AUTONOMIC SYMPTOMS	/	Nose obstruction
ADDITIONAL FINDINGS	Feeding difficulties Sleeping problems GERD Pharyngolaryngomalacia	ASD
BRAIN MRI	Bifrontal widened subarachnoid space	No abnormalities
AADC ENZYME ACTIVITY	<1.0 mU/L (reference values 16–99 mU/L)	1.8 mU/L (reference values 19–86 mU/L)
CEREBROSPINAL FLUID	HVA 56 nmol/L (reference values 324–1379 nmol/L) 5-HIAA 13 nmol/L (reference values 189–1380 nmol/L)	/

ASD = autism spectrum disorder; GERD = gastro-oesophageal reflux; HOM = homozygous.

Table 2
Overview of reported mild patients.

	Tay et al., 2007		Hasegawa et al., 2021		Leuzzi et al., 2015	
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**
Hypotonia	+	+	+	+	+	+
Other motor symptoms	Truncal dystonia	Dystonia left foot Lower limb hypertonia	–	–	Tremors, dystonia	Balance impairment
Developmental milestones	Head control at 12 m Sitting at 18 m Walking at 2.5y	Walking at 7y	Rolling over at 9 m Sitting at 16 m Walking at 23 m	Rolling at 4 m Sitting at 12 m Crawling at 14 m Walking at 30 m	Sitting at 3y Standing at 5y Walking at 7y	Walking at 5y
Oculogyric crises	+ (at 12y old)	+	+	+	+ (at 15y old)	+
ID	Mild	Mild	Mild	Mild	Mild	Mild
Speech development	Mild dysarthria	Mil dysarthria	Fluent communication	Fluent communication	Impaired	Mil dysarthria, bradylalia
Ptosis	+	+	+	+	+	+
Fatigue	+	+	+	Unknown	+	+
Sleep disturbance	+	+	–	–	Unkown	Unknown
Additional symptoms	Hypernasal speech Drooling	Drooling	Nasal congestion Drooling	Nasal congestion Drooling	Nasal speech Myoclonic jerks	Orthostatic hypotension Myoclonic jerks
CSF analyses	5-HIAA 13 nmol/L (67–189 nmol/L) HVA 64 nmol/L (167–563 nmol/L) 3-OMD 310 nmol (<100 nmol/L)	/	5-HIAA 2.5 ng/mL (16.1–32.6 ng/mL) HVA 13.3 ng/mL (27.3–153.1 ng/mL)	5-HIAA 4.4 ng/mL (19.2–54.8 ng/mL) HVA 27.3 ng/mL (40.3–166.5 ng/mL)	5-HIAA 30.3 nmol/L (45–135 nmol/L) HVA 124.3 nmol/L (98–450 nmol/L)	5-HIAA 50.4 nmol/L (45–135nmol/L) HVA 169.3 nmol/L (98–450 nmol/L)
AADC enzyme activity	<1 pmol/min/ml (36–129 pmol/min/ml)	<1 pmol/min/ml (36–129 pmol/min/ml)	/	/	Undetectable	Undetectable
Genetic findings	*DDC* c.853C > T p. (Arg285Trp) (Pat) + *DDC* IVS6+4A > T (Mat)	*DDC* c.853C > T p. (Arg285Trp) (Pat) + *DDC* IVS6+4A > T (Mat)	*DDC* c.202G > A p. (Val68Met) (Pat) + *DDC* c.254C > T p. (Ser85Leu) (Mat)	*DDC* c.202G > A p. (Val68Met) (Pat) + *DDC* c.254C > T p. (Ser85Leu) (Mat)	*DDC* c.105delC p. (Tyr37Thrfs*5) (Pat) + c.710T > C p. (Phe237Ser) (Mat)	*DDC* c.105delC p. (Tyr37Thrfs*5) (Pat) + c.710T > C p. (Phe237Ser) (Mat)

ID: Intellectual disability; CSF: Cerebrospinal fluid; 5-HIAA: 5-hydroxyindoleacetic acid; HVA: Homovanillic acid.

to AADC deficiency. Oculogyric crises are more prominent in the afternoon. He is currently treated with selegiline, trihexyphenidyl, melatonin and hydroxyzine. Treatment with pyridoxine was stopped since it was expected to have no significant effect on the low residual AADC plasma activity and due to the lack of clinical response. Under treatment: the dystonic and oculogyric crises are less severe and cause less discomfort.

2.2. Case 2

Our second case is a 15-year old boy of Turkish origin. His birth was unremarkable with Apgar scores of 10/10/10. He is the second child of non-consanguineous, healthy parents and has two healthy brothers.

The boy first presented at the age of six with mild intellectual disability (ID), language delay, fatigue and concentration problems. Clinical examination was normal with no dysmorphic features. A year later, a change in gait was noted with endorotation of both feet and flexion of elbows and wrists. He progressively experienced involuntary upward movements of the eyes with preserved consciousness. EEG and brain MRI were both normal. Genetic testing, including a karyotype, chromosomal microarray, repeat expansion of *FRAXA* (fragile X syndrome), *DMPK* (Myotonic dystrophy) and a panel containing 150 genes involved in epilepsy with/without ID, did not reveal any pathogenic variants.

At the age of 12 years, his gait abnormalities had deteriorated and were triggered by walking for >200 m and other types of exercise. The gait was characterised by extension and torsion of the head with tension mostly in the right arm and foot, which was reversible at rest. The dystonic crises were more present in the evening. His complaints of fatigue were present throughout the day. Additional genetic testing using trio WES with analysis of a gene panel for ID revealed a homozygous c.941T > C p. (Met314Thr) variant in the *DDC* gene (NM_001082971.2) that had not been described in the literature, which was absent from control databases (GnomAD, ESP) and predicted to be pathogenic by the majority of *in silico* prediction programs (supplement 1). Enzymatic testing showed high reduction of AADC plasma activity. A diagnosis of AADC deficiency was made, since the diagnostic criteria were fulfilled.

First, monotherapy with pyridoxine was started; pramipexole was added shortly after, which ameliorated the patient's symptoms with improvement of exercise intolerance and reduction of dystonic crises. An overview of the patient's clinical and genetic data can be found in Table 1.

3. Discussion

AADC deficiency is an autosomal recessive neurometabolic disorder with onset usually during the first months of life. Most patients present with a severe phenotype characterised by hypotonia, hypokinesia, dystonia, oculogyric crises, developmental delay and dysfunction of the autonomic nervous system. Up till now, only six mild cases have been described in literature, all sibling pairs. All these mild patients had a mild developmental delay and were able to reach most of their milestones before diagnosis was made and treatment was initiated. An overview of the clinical phenotype and diagnostic investigations of these patients can be found in Table 2.

The first case presented with a classic phenotype and an early presentation characterised by a pronounced developmental delay, hypotonia, dystonic crises, feeding and sleeping problems. This already led to the clinical suspicion of a neurotransmitter disorder, which was confirmed by the detection of a homozygous missense variant in *DDC*.

The second patient demonstrated an atypical presentation of AADC deficiency. The patient presented at a later age, with only mild ID and later with dystonic crises triggered by effort. This atypical presentation led to a delay in diagnosis – more than six years passed between the initial genetic test and his final diagnosis. Retrospectively, subtle signs of the disease were present earlier in life e.g. neonatal nasal congestion, upwards gaze at four months old, increasing in duration and frequency at later age, and inability to sit at 9 months, suggestive of hypotonia. These findings highlight the importance of a detailed medical history. The initial genetic evaluation in case 2, using a panel for epilepsy with/without ID, did not reveal any abnormalities. At that point in time, this panel did not contain the *DDC* gene.

In both cases, WES played a crucial role in the diagnosis. Both identified variants were missense variants that were not previously reported in patients with AADC deficiency (Table 1). Since the symptomatology of AADC deficiency is heterogeneous, the disorder can often be seen as a CP mimic. Therefore, WES based strategies are highly valuable to differentiate AADC deficiency from other disorders.

Therapy usually consists of a combination of multiple drug classes. The first-line treatments are pyridoxine, selective dopamine agonists (e.g. pramipexole) and monoamine oxidase (MAO) inhibitors (e.g. tranylcypromine). Generally, monotherapy of pyridoxine does not show a significant response. Hence, selective dopamine agonists are added at low doses and are raised stepwise. Symptomatic treatment is also of importance e.g. anticholinergic drugs for the treatment of autonomic symptoms, dystonia and oculogyric crises, melatonin in case of sleeping problems and benzodiazepines in prolonged dystonic or oculogyric crises [1,4]. For the second patient, the combination of pyridoxine and pramipexole led to a significant improvement with a major impact on quality of life, illustrating the importance of therapy initiation, even in milder cases. Finding a suitable therapy in the severely affected patient was much harder with only a slight improvement in his symptoms.

Gene therapy has become an area of interest in the treatment of AADC deficiency. A study from 2019 by Kojima et al. showed improvement in motor function and dystonic crises in six patients with a moderate to severe phenotype in whom a gene vector was injected bilaterally in the putamen. In addition, the gene therapy lead to almost complete disappearance of oculogyric crises in the moderate cases. On Positron Emission Tomography (PET) scan, an enhancement of intracranial AADC expression was seen up to two years after surgery [5]. So far, studies have demonstrated an acceptable tolerability and safety despite it being a quite invasive treatment [6]. However, more research is warranted to map the long-term effects of the treatment.

To conclude, AADC deficiency is a rare neurometabolic disorder characterised by a broad phenotypic spectrum with a combined

deficiency in serotonin, dopamine, adrenaline and noradrenaline. We expand the phenotype with the first report of exercise-induced dystonic crises. Given the phenotypic variability of this disorder, genetic testing using WES will in many cases be key to diagnosing this disorder, which in turn is crucial to initiate appropriate treatment. Despite the difficulties in finding the right drug combination, the correct treatment can undoubtedly have significant effects on the quality of life of AADC patients and their families.

Ethics statement

Written informed consent regarding the publication of clinical data and potentially identifiable images in this study was obtained from the patients' parents/legal guardians.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CRediT authorship contribution statement

Liene Thys: Conceptualization, Data curation, Funding acquisition, Writing – original draft, Writing – review & editing. **Marije Meuwissen:** Conceptualization, Supervision, Writing – review & editing. **Katrien Janssens:** Supervision, Writing – review & editing. **Diane Beysen:** Conceptualization, Data curation, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23746.

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