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ADULT-ONSET LEVODOPA-UNRESPONSIVE PARKINSONISM AS THE PRESENTING FEATURE OF AROMATIC L-AMINO ACID DECARBOXYLASE DEFICIENCY

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ABSTRACT

Introduction: Aromatic L-amino acid decarboxylase is a critical enzyme required for the final step in the synthesis of dopamine and serotonin, two important neurotransmitters. Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare autosomal recessive disorder of neurotransmitter biosynthesis caused by pathogenic variants in the dopa decarboxylase (*DDC*) gene. An absence or decrease of dopamine and serotonin levels may lead to severe motor and neurodevelopmental impairments. It classically presents within the first 6 months of life with a triad of hypotonia, oculogyric crises and developmental delay. Adult-onset presentations are extremely rare and underreported.

Case description: We report the case of a 53-year-old man who presented with progressive left-sided bradykinesia, stiffness, rigidity and resting tremor over a year and a half. Examination demonstrated asymmetrical parkinsonism including facial hypomimia, cogwheel rigidity and a reduced arm swing on the left. A trial of levodopa of up to 1000 mg levodopa equivalent daily dose did not improve his condition. Magnetic resonance imaging of the brain was reported as normal without radiological signs of atypical parkinsonian neurodegenerative disorders. An autoimmune and onconeural antibody panel was negative. The patient's symptoms progressively deteriorated and he noted dysphagia requiring a tailored feeding plan Dopamine transporter single-photon emission computed tomography was performed demonstrating a marked reduction of nigrostriatal synaptic integrity at the right putamen and modest reduction at the left putamen. Targeted genetic testing identified a homozygous missense variant [NM_000790.3: c.710T>C p. (Phe237Ser)] in the *DDC* gene, establishing the diagnosis of AADC deficiency. Levodopa was substituted with a direct dopamine agonist (ropinirole) which resulted in a modest clinical improvement; however, dose escalation was limited by nausea. The patient subsequently developed neuropsychiatric symptoms which were managed with mirtazapine and sodium valproate.

Conclusion: This case expands the recognised phenotypic spectrum of AADC deficiency and highlights the importance of considering neurotransmitter biosynthesis defects in levodopa-unresponsive adult parkinsonism.

KEYWORDS

Aromatic L-amino acid decarboxylase deficiency, *DDC* gene, levodopa-unresponsive, atypical parkinsonism, neurogenetics

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LEARNING POINTS

- Aromatic L-amino acid decarboxylase (AADC) deficiency, classically an infantile-onset neurometabolic disorder, can present in adulthood as a levodopa-unresponsive parkinsonian syndrome and should be considered in adults with otherwise unexplained atypical parkinsonism.
- In cases of lack of response to adequate doses of levodopa in an apparent Parkinson's disease phenotype, consideration of a neuroreceptor biosynthesis defect should be made and direct dopamine agonists such as ropinirole can be trailed, as they bypass this metabolic block, and may produce clinical improvement.
- Unremarkable magnetic resonance imaging does not exclude a neurodegenerative or genetic parkinsonism. Dopamine transporter single-photon emission computed tomography can demonstrate reduced uptake representing nigrostriatal denervation in AADC deficiency. Biallelic dopa decarboxylase molecular genetic testing is first line for diagnosis, guiding drug selection and genetic counselling of the patient and relatives.

INTRODUCTION

Aromatic L-amino decarboxylase (AADC) is an enzyme responsible for catalysing the final step in the biosynthesis of the neurotransmitters dopamine and serotonin, from L-3,4-dihydroxyphenylalanine and 5-hydroxytryptophan respectively[1,2] *(Fig.1)*. AADC is encoded by the dopa decarboxylase (*DDC*) gene on chromosome 7. Pathogenic variants in *DDC* lead to insufficient production of functional AADC[1]. Advances in genetic testing and increased awareness has led to identification of a range of phenotypes associated with *DDC*[3]. Presentation is classically in infancy with a triad of hypotonia, oculogyric crises and developmental delay[1,3,4]. Other reported symptoms include global dystonic and hypokinetic movement disorders and autonomic dysfunction. Over the last decade the phenotypic spectrum has been expanded to include adult populations, however these remain rare[5–7]. In this population, parkinsonism, dysphagia and mood disturbances can dominate the clinical picture. We report a case of a previously well 53-year-old man, in whom an 18-month history of levodopa-unresponsive parkinsonism, led to the identification of biallelic *DDC* variants and a diagnosis of AADC deficiency.

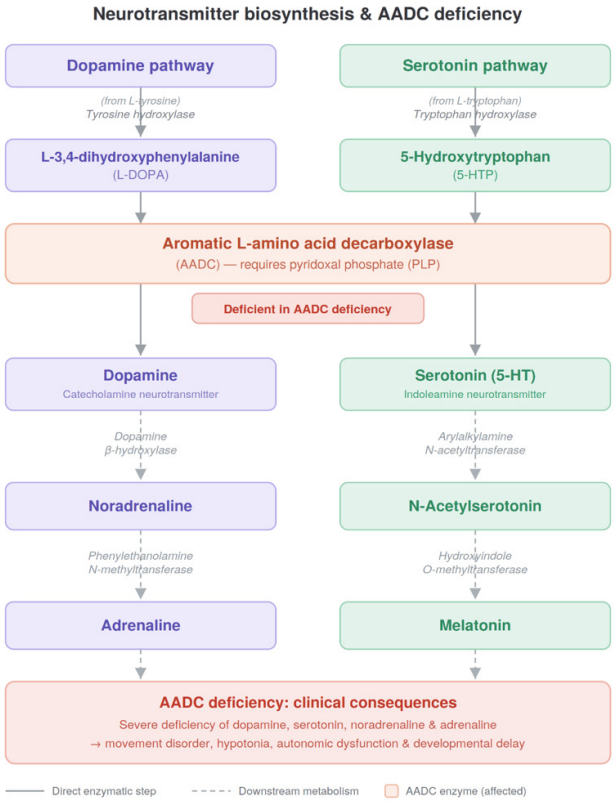
CASE DESCRIPTION

A 53-year-old previously independent man was referred to neurology with progressive parkinsonism. He reported an 18-month history of insidious, progressive asymmetrical bradykinesia and rigidity, more pronounced on the left side, accompanied by an ipsilateral resting tremor. Two months prior to referral, magnetic resonance imaging (MRI) of the brain was reported as normal. He also described intermittent choking episodes affecting both solids and liquids, suggestive of early bulbar involvement.

His medical history was notable only for irritable bowel syndrome. He had no known drug allergies and was taking levodopa/benserazide (Madopar), initiated prior to referral for presumed idiopathic Parkinson's disease. There was no relevant family history, and he denied smoking, alcohol consumption, or illicit drug use.

On examination, there was facial hypomimia, a left-sided resting tremor, bradykinesia, and cogwheel rigidity. Muscle power was preserved in all limbs. His vertical gaze saccades and pursuit were intact. Gait assessment demonstrated independent mobilisation with good stride length and turning, though there was reduced arm swing bilaterally. Postural stability was preserved. Given the early bulbar symptoms and poor response to dopaminergic therapy, atypical parkinsonism was suspected.

Neuroimaging, including prior MRI brain, reviewed at a national neurosciences multidisciplinary meeting, showed no features suggestive of atypical parkinsonian neurodegenerative disorders. A dopamine transporter single-photon emission computed tomography (DaT-SPECT) scan demonstrated markedly reduced nigrostriatal uptake in the right putamen, with modest reduction in the left putamen and preserved uptake in both caudate



| ***Figure 1.*** *Dopamine and serotonin biosynthesis pathway.*

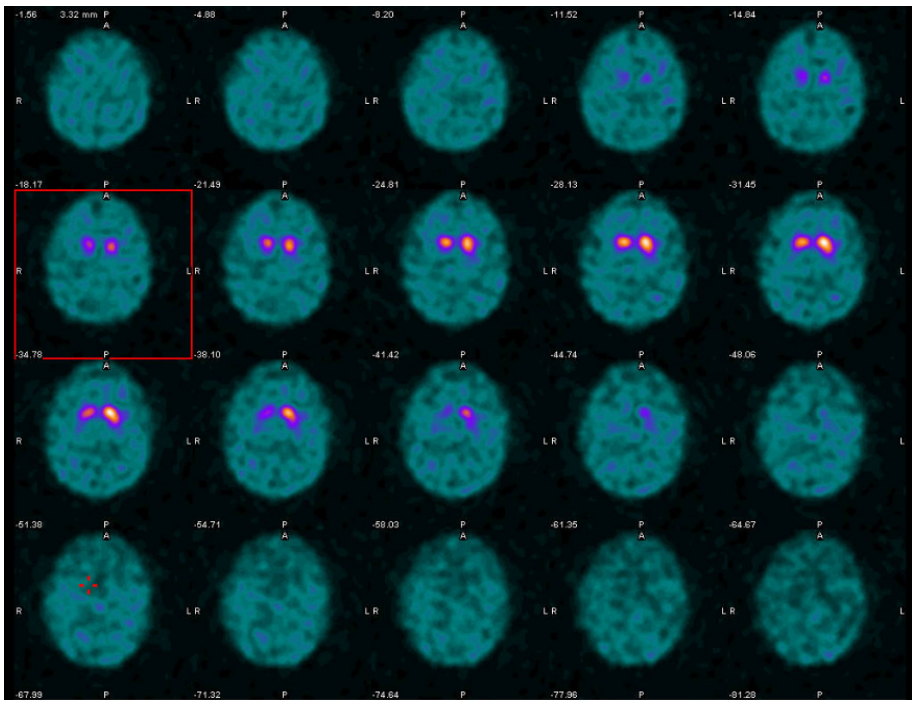


Figure 2. Dopamine transporter single-photon emission computed tomography scan showing markedly reduced nigrostriatal uptake in the right putamen.

Investigation	Result
Brain MRI (structural)	Reported as normal; no features of a Parkinson-plus syndrome
CT thorax, abdomen, pelvis	No occult malignancy identified
Onconeural antibodies	Negative
Anti-LGI1, anti-AMPA, anti-glycine receptor, anti-VGKC antibodies	All negative
Anti-GAD antibodies	Negative
Levodopa trial (up to 10 doses/day of levodopa/benserazide)	No clinical response
DaT-SPECT	Marked reduction in nigrostriatal synaptic integrity at the right putamen; modest reduction at the left putamen; preserved uptake at both caudate nuclei
Targeted DDC gene sequencing NM_000790.3	Homozygous pathogenic variant c.710T>C p.(Phe237Ser)

Table 1. Summary of key investigations.
Abbreviations: MRI, magnetic resonance imaging; CT, computed tomography; LGi1, leucine-rich glioma-inactivated 1; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; VGKC, voltage-gated potassium channel; GAD, glutamic acid decarboxylase; DaT-SPECT, dopamine transporter single-photon emission computed tomography; DDC, dopa decarboxylase.

nuclei, correlating with the predominantly left-sided motor features *(Fig 2)*. Extensive serological evaluation for autoimmune and paraneoplastic causes, including onconeural and neuronal surface antibodies, was negative *(Table 1)*. Additionally, following an unprovoked deep vein thrombosis, contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis showed no evidence of malignancy. Targeted next-generation genetic sequencing identified a homozygous missense variant [NM_000790.3:c.710T>C p.(Phe237Ser)] in the *DDC* gene. This was classified as likely pathogenic based on ACMG/AMP guidelines[8]. These genetic findings established the diagnosis of autosomal recessive aromatic L-amino acid decarboxylase deficiency. Follow- up genetic testing of the patient's mother confirmed her to be a heterozygous carrier of the variant. Testing on the patient's father was not possible.

Initial management involved escalation of levodopa therapy to 600 mg, and subsequently to 1000 mg levodopa equivalent daily dose, without clinical benefit. Withdrawal of dopaminergic therapy did not result in deterioration. Supportive therapies, including physiotherapy and speech and language input, were initiated early, with dietary modification due to dysphagia.

Following genetic diagnosis, treatment was revised with the introduction of a dopamine agonist (ropinirole), resulting in

improvement in bradykinesia and tremor. Dose titration to 5 mg three times daily was limited by nausea, with 3mg three times daily being well tolerated and clinically effective.

Over the following year, the patient remained neurologically stable on ropinirole alongside ongoing physiotherapy and speech therapy. However, he developed neuropsychiatric symptoms, including mood lability and anxiety, necessitating psychiatric intervention and treatment with mirtazapine and sodium valproate. At most recent follow-up, approximately two years after genetic diagnosis, he remained stable with no further motor deterioration and was able to maintain employment as a site inspector.

DISCUSSION

AADC deficiency is generally regarded as a paediatric neurometabolic disorder. In 2017 Wassenberg et al. published a consensus clinical guideline that describes the condition with symptoms onset typically early in life, with the key clinical symptoms of hypotonia, movement disorders and developmental delay[4]. A modified Delphi consensus in 2021 by Carlo Fusco et al. confirmed this and also included a rarer, milder phenotype of intellectual disability and autonomic dysfunction without dystonia or oculogyric crises, and spontaneous resolution in the second decade of life[10]. There are a small number of case reports of patients who have been diagnosed in adulthood worldwide, and this usually follows a lifelong history of milder neurological symptoms[1,5–7]. This case is a notable presentation of AADC deficiency due to an atypical phenotype and age at onset. Our patient reached the sixth decade of life with no significant neurological features or developmental delay, and his presenting phenotype was of atypical parkinsonism rather than the more characteristic dystonia which contributed to diagnostic delay.

One of the earliest reports regarding adult patients with AADC deficiency was published in 2015 by Leuzzi et al.[5] who reported two adult sisters with the same *DDC* variant as in our case: c.710T>C p.(Phe237Ser). These patients presented with myoclonic jerks, oculogyric crises, tremors and developmental delay during childhood. These symptoms improved spontaneously during adolescence and then re-presented in adulthood with asthenic and parkinsonian symptoms, which was when the pathogenic mutations on the DDC gene were detected. These patients also responded well to dopamine agonist therapy[5].

Parkinsonism poorly responsive to levodopa is an important feature in AADC deficiency and can be mechanistically explained through the pathophysiology of the condition. Oral administration of levodopa depends on the activity of AADC to catalyse levodopa into dopamine. Pathogenic variants in *DDC* will severely reduce AADC expression, resulting in supplemental oral levodopa remaining functionally inert[1,4]. This pathophysiology underpins the clinical rationale for the use of dopamine agonists as the pharmacological therapy of choice. This class of drugs work agonistically at the postsynaptic D2/D3 receptor and are not dependent on AADC levels, bypassing this enzymatic block entirely[1,4]. The 2021 Delphi consensus statement showed unanimous agreement regarding the use of dopamine agonists as the first-line therapeutic choice in AADC deficiency, alongside monoamine oxidase B inhibitors and vitamin B6[4,9]. The positive clinical response that our patient had when changing from levodopa to ropinirole is concordant with this and increased diagnostic certainty.

The findings on DaT-SPECT imaging are pertinent as such investigations are rarely described in cases of AADC deficiency. Brain imaging in classical infantile AADC deficiency is typically reported as normal or non-specific in the majority of cases[1,4] Asymmetric reduction in the nigrostriatal synaptic integrity more marked on the right correlated clinically with the left sided motor features. Whilst useful, DaT-SPECT is unable to discern between idiopathic Parkinson's disease and other atypical parkinsonian syndromes, including AADC. Specific investigations with an autoimmune antibodies panel including anti- glutamic acid decarboxylase, anti- leucine-rich glioma-inactivated 1, and anti-glycine receptors were taken to exclude autoantibody movement disorders which may present with parkinsonism and represent treatable causes that need to be excluded in the presence of a poor response to dopaminergic therapy[10]. The occurrence of an unprovoked deep vein thrombosis (DVT) raised the suspicion of an occult malignancy however cross-sectional imaging was normal and paraneoplastic antibodies were negative. The DVT could possibly be attributed to reduced mobility secondary to the parkinsonism.

The diagnosis was ultimately made through molecular genetic testing. Current consensus recommendations state that there are two pathways for making the diagnosis of AADC deficiency. As was the case in our patient, molecular genetic evidence of biallelic pathogenic variants of *DDC* alone is sufficient for diagnosis. Alternatively, a combination of characteristic cerebrospinal fluid (CSF) or plasma neurotransmitter profile, and reduced plasma AADC activity can be used. As the first criteria was satisfied in our case, further CSF and AADC activity analysis were deemed unnecessary[1,4].

This case highlighted the importance of prolonged follow-up with a multidisciplinary approach in patients with neurometabolic disorders. Speech and language pathology, and physiotherapy support were required throughout the course of follow-up, with a dynamic feeding regime employed throughout the course of his disease. Prolonged follow-up also provided insight to the long-term neuropsychiatric manifestations that relate to the combined dopamine-serotonin deficiency. Psychiatric complaints are well reported in the majority of paediatric cases, with patients suffering from mood disorders, anxiety and/or irritability [1,4]. Treatment options for these symptoms are also guided by the pathophysiology of AADC deficiency as dopamine receptor antagonists such as typical

antipsychotics are to be avoided since they may worsen the clinical picture[1,3].

CONCLUSION

This case adds to a small but growing literature base of atypical AADC phenotypes that present in the adult population. It highlights the need to consider aromatic L-amino acid decarboxylase deficiency as a differential in atypical Parkinson's disease, particularly when an adequate levodopa trial is ineffective. Targeted *DDC* molecular genetic testing is diagnostic and allows for targeted treatment adjustment to a direct dopamine agonist. Prolonged follow-up with a multidisciplinary team is essential to monitor for, and manage, neuropsychiatric complications as they arise.

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