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Mild dopa-responsive dystonia in heterozygous *tyrosine hydroxylase* mutation carrier: Evidence of symptomatic enzyme deficiency?

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ABSTRACT

We present a case of mild, adult-onset dopa-responsive dystonia (DRD) with a heterozygous mutation in the tyrosine hydroxylase (*TH*) gene. We propose that this genetic state may have led to partial enzyme deficiency. Future studies should attempt to identify and characterize the phenotype of other patients with single *TH* variants.

1. Manuscript

Dopa-responsive dystonia (DRD) refers to a group of hereditary dystonias that improve with levodopa. Heterozygous mutations affecting the guanosine triphosphate cyclohydrolase (*GCH1*) gene cause the most common and mildest form of DRD, with dystonic features typically manifesting in childhood. Autosomal recessive *GCH1* cases tend to be more severe [1]. Biallelic mutations in the sepiapterin reductase (*SPR*), 6-pyruvoyl tetrahydropterin (*PTP*) synthase and tyrosine hydroxylase (*TH*) genes typically lead to more severe phenotypes and present earlier in life. In *TH* deficiency, isolated dystonia is uncommon; patients have parkinsonism and/or a complex disorder combining dystonia, other movement disorders (tremor, myoclonus, oculogyric crisis) plus additional features [1]. Patients with *TH* deficiency have previously been classified as either type A which manifests in the first few years of life (range 2 months–5 years) and is characterized by a progressive hypokinetic-rigid syndrome with dystonia, or type B which manifests sooner after birth (range 0–3 months) with a more complex encephalopathy (including the varied movements disorders described above plus intellectual impairment and autonomic dysfunction) [2]. Here, we report a patient with mild, adult-onset DRD with two heterozygous variants on the same allele of the *TH* gene. Written informed consent for publication was obtained from the patient.

A 65-year-old man developed left foot dystonia without diurnal fluctuations aged 38 years. There was no history of other complaints such as oculogyric crises or autonomic dysfunction. Two years later, levodopa-carbidopa 100/25mg 1 tablet once daily resulted in a dramatic and sustained response, allowing him to continue working as a post-office courier until his planned retirement. He had no problems with motor dexterity. He retained mildly abnormal posturing of his fingers, mild stiffness of his legs (particularly on the left side), neither of which improved with higher levodopa dosage. On three occasions, levodopa withdrawal resulted in gradual re-emergence of foot dystonia over months. He never developed dyskinesias or motor fluctuations in response to levodopa.

He had no children. His deceased father, examined in his 80s, had some jerky hand movements but no neurological diagnosis was made. His deceased mother had isolated excessive eye blinking throughout most of her adult life.

When last examined, he had clawing of the toes, left-sided jerks of individual fingers, semi-rhythmic movements of the hands when arms were outstretched (consistent with dystonic tremor), mildly increased tone in both upper limbs, but no bradykinesia. Gait was normal.

Fluorodopa PET imaging performed aged 41 was normal. The patient declined CSF neurotransmitter testing. No mutations in *GCH1* or *SPR* genes were found. The *GCHI*, *TH*, and *SPR* genes were analyzed by PCR and sequencing of both DNA strands of the entire coding region and the highly conserved exon-intron splice junctions. Multiplex ligation-dependent probe amplification (MLPA) analyses were performed for *GCHI* and *TH*. *TH* gene analysis showed a pathogenic variant (c.296del [p.Leu99Argfs*15]) and a variant of uncertain significance (c.1169C > T [p.Ser390Leu]), which were confirmed to be present on the same allele using a comprehensive third-generation sequencing approach (see Supplemental Methods).

To our knowledge, only biallelic *TH*-DRD cases have been reported to date [3]. A 2010 study described 36 *TH*-DRD cases and reviewed all previously published cases: the oldest age of onset was 5 years [2]. Since then, others have reported onset at older ages (7, 12 and 18 years) [3–5]. If the present *TH* mutation is the cause of our patient's DRD, he has by far the oldest age of onset and is the only one with a mild phenotype of isolated dystonia resembling *GCH1*-DRD.

As in some other recessive disorders, we hypothesize that heterozygosity in *TH*-DRD could lead to a benign form of a typically severe disease, possibly due to a mild reduction in TH activity. Supporting this hypothesis, a small but significant reduction in striatal levodopa was observed in the post-mortem brain tissue of a heterozygous knock-in mouse model replicating a human *TH* mutation, as opposed to the profound reduction seen in the homozygous mouse model, demonstrating that the effect may be dependent on gene dosage [6]. Further studies of adult-onset DRD cases without *GCH1* mutations may identify similar cases and provide further insights into the genetic spectrum of this condition.

2. Authors' roles

Julien F. Bally: Conception, Organization, Execution, Writing of the

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CK: serves as a medical consultant to Centogene for genetic testing in the field of movement disorders and dementia, excluding Parkinson's disease. Stock Ownership in medically-related fields: None. Advisory Boards: Advisory Boards. Partnerships: None. Honoraria: Annals of Neurology (Associate Editor). Grants: DFG, BMBF, EU, MJFF, CCXDP. Intellectual Property Rights: None. Expert Testimony: None. Employment: University of Luebeck. Contracts: None. Royalties: Oxford University Press. Other: None.

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Declaration of competing interest

The manuscript has not been previously published and is not under review at any other journal. No other related work is under submission elsewhere. All authors of the paper have participated to the study, revised the manuscript and approved the final version of the manuscript. There is no ghost writer. There is no financial or any other type of conflict of interest related to the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2020.01.017.

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