Anxiety and depression in tyrosine hydroxylase deficiency: a case report

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ABSTRACT

Background: Tyrosine hydroxylase (TH) deficiency is a very rare genetic disorder of monoamine synthesis which - alongside Guanosine triphosphate (GTP) cyclohydrolase deficiency - is one of the metabolic dopa-responsive dystonias. These disorders classically present as a dystonia with onset in adolescence which is non-progressive and responds to standard dopaminergic treatment: however, little is known about the relationship between TH deficiency and psychiatric illness.

Case Presentation: We describe a case of a young woman who, in the absence of any heralding psychiatric symptomatology of any nature, developed a severe and limiting panic disorder at around the time of onset of her movement disorder in the setting of TH deficiency, which impacts dopamine synthesis.

Conclusion: Neurometabolic disorders that affect neurotransmitter function frequently present with psychiatric symptomatology and can provide models for understanding some frequently presenting psychiatric illnesses such as depression and anxiety. We discuss the interplay between the dopaminergic and serotonergic systems, and how an ostensibly dopaminergic disorder could produce what has long been understood to be a serotonergically-driven anxiety syndrome.

Keywords: Tyrosine hydroxylase, anxiety, panic disorder, depression, case report.

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Case Presentation

An 18-year-old single student without a previous history of psychiatric illness or substance abuse was referred to a neuropsychiatry service for an assessment of psychiatric symptoms associated with a diagnosis of dopa-responsive dystonia (DRD) secondary to tyrosine hydroxylase (TH) deficiency. She had no issues with pregnancy nor delivery, had normal motor and intellectual development, and her only other significant medical history was an ovarian cyst removal. She described the onset of symptoms at the age of 17 with significant anxiety regarding her studies, a low mood and poor motivation; she was originally treated with psychotherapy without benefit. Four months later, she noted oculogyric movements occurring predominantly with exercise and lasting up to 1 hour, accompanied by increasing stiffness and deterioration in her gait with loss of balance. A combined rest/action tremor also developed, predominantly in her hands, and worsened with anxiety. She had noted a more generalized anhedonia associated with periods of low mood, initial insomnia, and loss of appetite. Her first panic episode was triggered by an oculogyric crisis and was associated with typical physiological symptoms including shortness of breath, tachycardia and diaphoresis, and occurred every 1 to 2 weeks.

Her 25-year-old sister had a similar presentation at the age of 21 with whole body rigidity, oculogyric crises, and had been troubled significantly with anxiety and mood changes. Motor symptoms responded to levodopa and she takes benserazide in addition to escitalopram. Her diagnosis was genetically confirmed.

The patient was assessed at a neurogenetics clinic, which confirmed the diagnosis of autosomal recessive TH deficiency causing her DRD. She was confirmed as a compound heterozygote for c.698 G > A and 1493A > G, located in exons 6 and 14, respectively, of the TH gene, mirroring those seen in her sister. The diagnosis was of panic disorder and major depression secondary to TH deficiency.

The patient received treatment with levodopa, improving her motor symptoms although her anxiety did not respond. Six months later, she began treatment with the serotonergic antidepressant escitalopram, initially at 5 and then 10 mg. She noted a significant improvement

in anxiety, and her panic episodes were much less frequent and severe, at 6 weeks. Moreover, sleep initiation improved and her family noted an increase in social engagement and motivation. She escalated dose to 20 mg and at this dose, panic episodes abated entirely. She has remained on this dose for 4 years.

Discussion

TH, an aromatic amino acid hydroxylase, catalyzes the conversion of tyrosine to levodopa, the precursor of catecholamines dopamine, adrenaline, and noradrenaline (Figure 1). TH deficiency is an exceedingly rare recessive neurometabolic disorder due to mutations in the TH gene, located on chromosome 11p15.5, with less than one hundred historical cases reported worldwide. Heterozygotes are generally asymptomatic, but in homozygotes presents with a broad phenotypic spectrum. In the mild form, called TH-deficient DRD, initial symptoms may be limited to lower-limb dystonia and/or gait difficulty. Bradykinesia and tremor can be observed and in general there is a progression to generalized dystonia. The early postnatal period is asymptomatic and onset of symptoms is generally between the age of 12 months and 12 years [1]. TH-deficient DRD patients usually demonstrate highly responsive symptoms with low doses of levodopa within the first 2 weeks of treatment [2] without significant motor adverse effects after chronic therapy [3].

Severe forms of TH deficiency are known as "TH-deficient infantile parkinsonism with motor delay" and "TH-deficient progressive infantile encephalopathy". These forms of the disorder appear soon after birth and are more difficult to treat. Treatment improvement with levodopa usually is slow and often limited by intolerable dyskinesias [2,4,5]. Some less typical clinical presentations of TH deficiency have also been reported, such a case with dopa responsive myoclonus dystonia and early-onset spastic paraplegia [6].

Diagnosis of TH deficiency relies on clinical suspicion, low cerebrospinal fluid levels of catecholamine metabolites (such as homovanillic acid), and normal concentrations of tetrahydrobiopterin (BH4), a cofactor for both tyrosine and tryptophan hydroxylases. Definitive diagnoses are established by molecular genetic testing. Approximately 60 TH pathogenic variants have been reported in individuals with TH deficiency [1]. Mutations that cause complete loss of TH activity are not compatible with life in knockout mice [7].

The largest cohort of TH deficiency cases was reported by Willemsen et al. [2], with 36 patients. The majority (69%) suffered a mild form of TH deficiency. Most of the patients affected by the mild form (67%) had normal cognitive capacities, while in the more severe forms 91% were mentally retarded.

Anxiety and depressive disorders are not uncommon in another DRD, namely autosomal-dominant GTP cyclohydrolase deficiency, which is a disorder of BH4 synthesis, a co-factor in all monoamine synthesis (serotonin in addition to catecholamines) [8]. In TH deficiency, however, the enzymatic deficiency is largely restricted to synthesis of catecholamines (which may be expected to predispose an individual to depressive symptomatology), but not serotonin, a monoamine crucially implicated in anxiety disorders. Given this, it is not immediately obvious why our patient and her sister presented with a clear panic disorder.

Several studies have demonstrated that serotonin has an important role in the neurobiology and treatment of panic disorder. It has been proven that a decrease in serotonin synaptic availability increases susceptibility to panic disorder, although it is still not known whether serotonin deficit is due to a deficit in its synthesis or neurotransmission, if its deficiency is a primary factor in the genesis of panic disorder or if serotonin has protective or modulatory influence on other excitatory neurotransmission systems, such as norepinephrine or cholecystokinin that may be able to trigger panic attacks [9].

Alternatively, there is the possibility that long-term treatment with levodopa could theoretically induce a secondary change to serotonin turnover and metabolism. Levodopa can impact serotonin metabolism due to its conversion to dopamine via aromatic amino acid decarboxylase, which also synthesizes serotonin from 5-hydroxytryptophan; theoretically, levodopa could

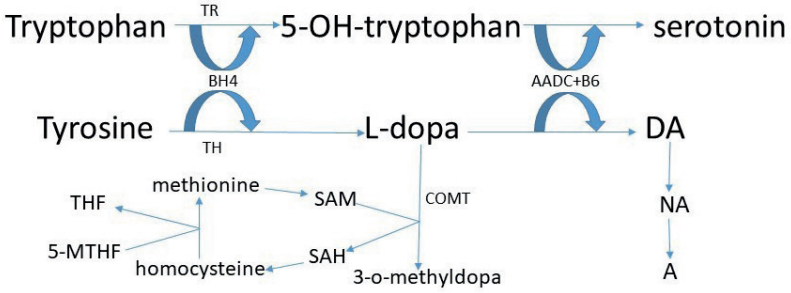

Figure 1. *Metabolic pathway: TR, tryptophan hydroxylase; TH, tyrosine hydroxylase; BH4 tetrahydrobiopterin; AADC, aromatic L-amino-acid decarboxylase; COMT, catechol-O-methyltransferase; NA, noradrenaline; A, adrenaline; 5-MTHF, 5-methyltetrahydrofolate; THF, tetrahydrofolate; SAM, S-adenosyl-L-methionine; SAH, S-adenosyl-L-homocysteine.*

thus act as a chronic competitive inhibition of serotonin metabolism. Moreover, depleted availability of 5-methyltetrahydrofolate as a consequence of excess formation of 3-methyldopa from long-term treatment with levodopa could be associated with reduced turnover of serotonin and dopamine in these individuals [10]. Furthermore, there is preclinical evidence that dopamine depletion alone can play a critical role in anxiety-related behavior [11,12].

Schiller et al. [3] reported a case of TH deficiency with mild cognitive impairment who developed panic attacks after receiving long-term treatment with levodopa, and which ceased within few days when the medication was ceased - although his motor symptoms worsened. However, our patient's onset of significant anxiety predated any treatment with levodopa and its initiation did not appear to materially affect her anxiety. In this case, other explanations should also be considered, some anxiety symptoms could resemble those presented in the autonomic dysfunction that can been observed in TH deficiency or could have appeared as a result of psychological condition due to the diagnosis of this disorder. However, the clear subjective sensation of intense anxiety and panic in this patient strongly suggests panic disorder over and above an autonomic response alone.

Conclusion

In TH deficiency, the presentation of a panic episode prior to dopaminergic treatment suggests that the long-term catecholamine deficit in these patients may produce secondary changes in serotonin metabolism and turnover that may predispose patients to anxiety disorders.

What is new?

The authors discuss the interplay between the dopaminergic and serotonergic systems, and how an ostensibly dopaminergic disorder could produce what has long been understood to be a serotonergically-driven anxiety syndrome.

List of Abbreviations

BH4	Tetrahydrobiopterin.
DRD	Dopa-responsive dystonia.
TH	Tyrosine hydroxylase.

Conflict of interests

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Consent for publication

Informed consent was obtained from all individual participants included in the study.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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References

1. Furukawa Y, Kish S. Tyrosine hydroxylase deficiency. 2017 [cited 2018 Jan 14] Available from: https://www.ncbi.nlm.nih.gov/books/NBK1437/
2. Willemsen MA, Verbeek MM, Kamsteeg EJ, de Rijk-van Andel JF, Aeby A, Blau N, et al. Tyrosine hydroxylase deficiency: a treatable disorder of brain catecholamine biosynthesis. Brain. 2010 Jun;133(Pt 6):1810–22. https://doi.org/10.1093/brain/awq087
3. Schiller A, Wevers RA, Steenbergen GC, Blau N, Jung HH. Long-term course of L-dopa-responsive dystonia caused by tyrosine hydroxylase deficiency. Neurology. 2004;63(8):1524–6. https://doi.org/10.1212/01.WNL.0000142083.47927.0A
4. Pons R, Syrengelas D, Youroukos S, Orfanou I, Dinopoulos A, Cormand B, et al. Levodopa-induced dyskinesias in tyrosine hydroxylase deficiency. Mov Disord. 2013;28(8):1058–63. https://doi.org/10.1002/mds.25382
5. Leuzzi V, Mastrangelo M, Giannini MT, Carbonetti R, Hoffmann GF. Neuromotor and cognitive outcomes of early treatment in tyrosine hydroxylase deficiency type B. Neurology. 2017;88(5):501–2. https://doi.org/10.1212/WNL.0000000000003539
6. Giovanniello T, Leuzzi V, Carducci C, Carducci C, Sabato ML, Artiola C, et al. Tyrosine hydroxylase deficiency presenting with a biphasic clinical course. Neuropediatrics. 2007;38(4):213–5. https://doi.org/10.1055/s-2007-991151
7. Zhou QY, Quaife CJ, Palmiter RD. Targeted disruption of the tyrosine hydroxylase gene reveals that catecholamines are required for mouse fetal development. Nature. 1995;374(6523):640–3. https://doi.org/10.1038/374640a0
8. Van Hove JL, Steyaert J, Matthijs G, Legius E, Theys P, Wevers R, et al. Expanded motor and psychiatric phenotype in autosomal dominant Segawa syndrome due to GTP cyclohydrolase deficiency. J Neurol Neurosurg Psychiatry. 2006;77(1):18–23. https://doi.org/10.1136/jnnp.2004.051664
9. Maron E, Shlik J. Serotonin function in panic disorder: important, but why? Neuropsychopharmacology. 2006;31(1):1–11. https://doi.org/10.1038/sj.npp.1300880
10. Surtees R, Heales S, Bowron A. Association of cerebrospinal fluid deficiency of 5-methyltetrahydrofolate, but not S-adenosylmethionine, with reduced concentrations of the acid metabolites of 5-hydroxytryptamine and dopamine. Clin Sci (Lond). 1994;86(6):697–702. https://doi.org/10.1042/cs0860697
11. Ogata M, Akita H, Ishibashi H. Behavioral responses to anxiogenic tasks in young adult rats with neonatal dopamine depletion. Physiol Behav. 2019;204:10–9. https://doi.org/10.1016/j.physbeh.2019.02.006
12. Espejo EF. Selective dopamine depletion within the medial prefrontal cortex induces anxiogenic-like effects in rats placed on the elevated plus maze. Brain Res. 1997;762 (1-2):281–4. https://doi.org/10.1016/S0006-8993(97)00593-3

Summary of the case

1	**Patient (gender, age)**	Female, 18 years
2	**Final diagnosis**	DRD secondary to TH deficiency. Panic disorder
3	**Symptoms**	Oculogyric movements, stiffness, loss of balance, rest/action tremor, anhedonia, low mood, initial insomnia, loss of appetite, panic episodes, anxiety
4	**Medications**	Levodopa and escitalopram
5	**Clinical procedure**	Genetic diagnosis
6	**Specialty**	Neuropsychiatry