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Dopa-Responsive Dystonia: Guanosine Triphosphate Cyclohydrolase 1, Tyrosine Hydroxylase, and Sepiapterin Reductase

Dear Editor,

We read the article entitled "Nephrocalcinosis in genetically proved dopa-responsive dystonia (DRD) due to sepiapterin reductase (SPR) deficiency in a Libyan girl" in this Journal with great interest. Etarhuni *et al*. reported the case of a female with DRD secondary to SPR deficiency who also presented nephrocalcinosis.[1] This unique characteristic was not already reported in other individuals affected by this pathology.

DRD is a very rare (1 in 1 million people) inherited type of dystonia that typically begins during childhood but may begin in adolescence or adulthood. DRD may be caused by the mutations in the guanosine triphosphate cyclohydrolase 1, tyrosine hydroxylase (TH), SPR genes, or the cause may be unknown. These genes are related to the enzymes that are associated with a common pathway responsible for the production of dopamine and serotonin (TH is not related).[2] The deficiency of dopamine can lead to a disbalance on the nigrostriatal area leading to dystonia and parkinsonism, mainly in the lower limbs,[3] where the most common clinical manifestation is tip-toe walking. A special type of DRD is the Segawa disease (DYT5 dystonia), which is dopa-responsive generalized dystonia, caused by abnormalities of the gene GCH-1 located on chromosomes 14q22.1–q22.2.[2]

We provided Figure 1 to remember the main metabolic pathway related to DRD. Table 1 is a resume of the main characteristics of the DRD due to SPR deficiency cases from the Middle Eastern and North Africa region.[1,4,5] It is interesting to observe that the majority of the patients manifested symptoms during infancy and early childhood. The main clinical presentation was dystonia in the lower limbs, in which the majority had tiptoe walking. Some individuals had unique characteristics such as generalized Parkinsonism, postural tremor, fast fatigability, equinovarus deformity, oculogyric crisis, permanent limb hypertonia, mild cognitive delay, and bilateral nephrocalcinosis. It is worthy of mentioning that the earlier the disease begins, the greater the impairment; also, the cognitive decline is sometimes refractory to treatment.[5]

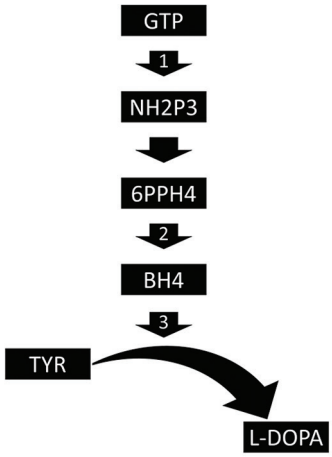

Figure 1: Metabolic pathways of neurotransmitters related to DRD. GTP: guanosine triphosphate, NH2P3: dihydroneopterin triphosphate, 6PPH 4: 6 pyruvoyl tetrahydropterin, BH4: tetrahydrobiopterin, TYR: Tyrosine, 1: GTP cyclohydrase 1, 2: SPR, 3: Tyrosine hydroxylase

The association of DRD due to SPR deficiency and nephrocalcinosis may be new, but the deposition of calcium in the renal parenchyma and dystonia was already reported with Lesch–Nyhan syndrome (hypoxanthine-guanine phosphoribosyl-transferase deficiency).[6] One clinical clue is the localization of dystonia because lower limbs are more commonly associated with DRD. Moreover, the presence of dystonia should be evaluated by a specialist to classify accordingly sometimes other diseases such as adrenoleukodystrophy can present with dystonia[7] or even the dystonia could be a benign finding that resolves without treatment.[8]

Authors' contributions

Equal.

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Conflicts of interest

There are no conflicts of interest.

Table 1: Dopa-responsive dystonia due to sepiapterin reductase deficiency cases from the Middle Eastern and North Africa region

Reference	Country	Age (years), sex	Onset	Clinical presentation	SPR variant	Management	Note
Shalash *et al*.	Egypt	32, female	Childhood	Lower limb DTN	c. 207C>G (p.Asp69Glu)	Good response. Benefit with L-DOPA and continued on pramipexole	-
		27, female	Childhood	Lower limb DTN	c. 207C>G (p.Asp69Glu)	Good response. L-DOPA, anticholinergics, amantadine	Generalized parkinsonism
		21, male	Puberty	Tiptoe walking	c. 207C>G (p.Asp69Glu)	Good response. Benefit with L-DOPA and continued on pramipexole	Postural tremor
		10, female	Childhood	Tiptoe walking	c. 207C>G (p.Asp69Glu)	No treatment was started	Fast fatigability
		5, male	Infancy	Tiptoe walking	c. 207C>G (p.Asp69Glu)	No treatment was started	Equinovarus deformity
AlSubhi *et al*.	Saudi Arabia	1.25, male	Infancy (3 months)	Axial hypotonia, DTN, and cognitive impairment	c. 527C>T (p.Ala176Val)	Good response. L-DOPA/carbidopa and 5-hydroxytriptophan	Oculogyric crisis
		7.5, fale	Infancy (3 months)		c. 527C>T (p.Ala176Val)	Good response. L-DOPA/ carbidopa	Oculogyric crisis
		16.5, male	Infancy (6 months)		c. 1A>G (p.Met1Val)	Good response. L-DOPA/ carbidopa	Permanent limb hypertonia
		6, female	Infancy (6 months)		c. 1A>G (p.Met1Val)	Good response. L-DOPA/ carbidopa	Permanent limb hypertonia
		9, male	Infancy (12 months)		c. 370 T>C (p.Trp124Arg)	Good response. L-DOPA/ carbidopa	Mild cognitive delay
Etarhuni *et al*.	Libya	12, female	Childhood (8 years)	Tip-toe walking	c. 207C>G (p. Asp69Glu)	No response. L-DOPA/ benserazide	Bilateral nephrocalcinosis

DTN: Dystonia, SPR: Sepiapterin reductase

Compliance with ethical principles

Not required.

Jamir Pitton, Ana Letícia Fornari Caprara

Department of Medicine, Federal University of Santa Maria, Santa Maria, Rio Grande do Sul, Brazil

Address for correspondence: Dr. Jamir Pitton, Rua Roraima, Santa Maria, Rio Grande do Sul, Brazil.
E-mail: jamirrissardo@gmail.com

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References

1. Etarhuni SA, Zeglam AM, Elbouaishi AS, Sharfddin AM. Nephrocalcinosis in genetically proved dopa-responsive dystonia due to sepiapterin reductase deficiency in a Libyan Girl. Ibnosina J Med Biomed Sci 2020;12:315-9.
2. Mishra S, Mallick AK, Panigrahy D, Nayak P, Biswal NR. Series of dopa responsive dystonia masquerading as other diseases with short review. J Pediatr Neurosci 2020;15:421-5.
3. Rissardo JP, Caprara AL. Mirtazapine-associated movement disorders: A literature review. Tzu Chi Med J 2020;32:318-30.
4. Shalash AS, Rösler TW, Müller SH, Salama M, Deuschl G, Müller U, *et al*. c. 207C>G mutation in sepiapterin reductase causes autosomal dominant dopa-responsive dystonia. Neurol Genet 2017;3:e197.
5. AlSubhi S, AlShahwan S, AlMuhaizae M, AlZaidan H, Tabarki B. Sepiapterin reductase deficiency: Report of 5 new cases. Eur J Paediatr Neurol 2017;21:583-6.
6. Banerjee S, Sinha SK, Varshney PG, Ahuja P. Anaesthetic management of a child with Lesch Nyhan syndrome. Indian J Anaesth 2019;63:1051-2.
7. Rissardo JP, Caprara AL. Dystonia and adrenoleukodystrophy: An overview. Ann Mov Disord 2020;3:65-6.
8. Kulkarni SD, Kothari SR. Pediatric movement disorders and neuromodulation: An overview. Neurol India 2020;68:S206-12.

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