Dystonia related to the GCH1 gene presented with motor and nonmotor symptoms

Distonia relacionada ao gene GCH1 apresentando-se com sintomas motores e não motores

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ABSTRACT

Background: Dopa-responsive dystonia (DRD) comprises a group of monogenic disorders with a frequently challenging diagnosis. Clinical manifestations include both motor and non-motor symptoms, the latter often being underrecognized.
Case report: A 50-year-old woman presented with involuntary movements of the feet (dystonia), leading to progressive gait impairment, without diurnal fluctuation. She also had a history of chronic recurrent depression since childhood. Genetic testing confirmed DRD. Treatment with L-dopa and fluoxetine resulted in satisfactory symptom control.
Discussion: DRD is commonly caused by mutations in GCH1, affecting tetrahydrobiopterin synthesis, a cofactor essential for catecholamine production, which explains both motor and psychiatric manifestations related to this condition.
Conclusion: We emphasize the importance of investigating non-motor symptoms in DRD, considering that this can lead to greater morbidity related to this condition, requiring specific treatment.

Keywords: Dystonia; Depressive Disorder; Genetics; Levodopa.

RESUMO

Fundamentos:
A distonia dopa-responsiva (DDR) compreende um grupo de doenças monogênicas com diagnóstico frequentemente desafiador. As manifestações clínicas incluem sintomas motores e não motores, sendo estes últimos muitas vezes subdiagnosticados.
Relato do caso: Mulher de 50 anos, iniciou movimentos involuntários nos pés (distônicos), cursando progressivamente com alteração da marcha, sem flutuação diurna. Apresentava ainda histórico de depressão crônica recorrente desde a infância. O teste genético confirmou DDR. O tratamento com levodopa e fluoxetina resultou em controle satisfatório dos sintomas.
Discussão: A DDR é mais comumente causada por mutações no gene GCH1, que afetam a síntese de tetrahidrobiopterina, um cofator essencial para a produção de catecolaminas, o que explicaria manifestações motoras e psiquiátricas associadas a essa condição.
Conclusão: Ressaltamos a importância da investigação dos sintomas não motores na DDR tendo em vista resultar em maior morbidade relacionada a esta condição com tratamento específico.

Palavras-chave: Distonia; Transtorno Depressivo; Genética; Levodopa.

ARTICLE INFO

DOI: https://doi.org/10.46979/rbn.v61i4.72028

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Conflict of interest - The authors have no conflict of interest to declare.

Financial Support: This work has not received any contribution grant or scholarship.

Authors' contributions:

BA and MB: data acquisition and writing; WNS: genetic analysis and writing; CP, DVN and LFV: analysis, editing and supervision.

All authors approved the final version of the manuscript and are responsible for all aspects of the work.

INTRODUCTION

Dopa-responsive dystonia (DRD) encompasses a group of monogenic disorders whose diagnosis can be challenging. The first report by Segawa and colleagues in 1976 described nine cases of hereditary dystonic syndrome with childhood onset, marked diurnal fluctuation, and dramatic improvement after L-dopa administration. At that time, the authors defined the condition as a progressive hereditary disorder of the basal ganglia. Since then, accumulated knowledge of the disease has improved understanding of the relationship between its genetic aspects and clinical presentations, and has led to the recognition of additional features, such as non-motor symptoms.

We present a case of DRD confirmed by genetic test that presented motor and non-motor symptoms related to it.

CASE REPORT

A right-handed 50-year-old woman noticed at age 7 that her feet moved involuntarily, with slight gait impairment, until age 15, when the movement worsened, and she began using unilateral support to walk. At age 20, she began with right-hand movements, without significant impairment in her activities. Fluctuations throughout the day were absent. The patient denied neuropsychomotor developmental delay or other movement disorders. She also had a diagnosis of chronic recurrent depression and had been taking antidepressants for several years, currently using fluoxetine 40 mg/day. Past personal medical history included heart surgery for interatrial communication, nontoxic multinodular goiter, and pernicious anemia. With non-consanguineous parents, the patient reported two siblings and a cousin with a similar condition, including depressive symptoms. In the third decade of life, after neurological examination, low-dose L-dopa (100mg/day) was prescribed with a significant response. The definitive genetic diagnosis was achieved in her fifth decade of life, with a GCH1 gene mutation (rare variant c.626+2dup) in heterozygosis. Since L-dopa treatment, the symptoms have remained stable, and no dose increase has been requested, nor have adverse effects occurred. The patient reports involuntary foot movements and loss of balance when not taking medication. The neurological exam, under L-dopa effect, shows intermittent bilateral toe athetosis, brisk tendon reflexes, bilateral extensor plantar responses, and an atypical gait with preserved coordination.

DISCUSSION

The genetic basis of DRD was well understood through analysis of the guanosine triphosphate cyclohydrolase-1 (GCH1) gene[1], located on chromosome 14q22.1-q22.2[2]. Although other genes have been associated with DRD, GCH1 is the most frequently affected[3]. GCH1 is responsible for the synthesis of GTP cyclohydrolase I (GTP-CH1), a protein involved in the biosynthetic pathway of tetrahydrobiopterin (BH4). BH4 is a critical cofactor for tyrosine hydroxylase (TH), the enzyme responsible for catecholamines (dopamine, norepinephrine, and epinephrine) production. BH4 has two other functions: it is a cofactor for phenylalanine hydroxylase (PAH) that converts phenylalanine into tyrosine in the liver (a necessary step in the amino acid metabolism); and participates in the synthesis of nitric oxide, a vasodilator and neurotransmitter[4]. Defects in the GCH1 gene result in dopamine deficiency in the striatum[5], although nigrostriatal degeneration is not identified. Biochemical evaluation in autopsies revealed reduced striatal dopamine in DRD, associated with decreases in BH4 and TH, without loss of nerve terminals, which excludes a neurodegenerative nature of the disease [6].

GCH1 gene defects can have autosomal dominant (AD) or recessive (AR) inheritance. AD with heterozygous variants is the most common form of DRD. AD-DRD shows reduced penetrance and highly variable expressivity[1]. AD-DRD patients display the classical picture as described by Segawa: childhood-onset lower limb dystonia, diurnal fluctuation, subsequent generalization, and reasonable response to L-dopa, even in tardive diagnosis and in delayed treatment[3]. This is attributed to residual TH enzymatic activity in these patients, arising from the reduction (but not suppression) of GTP-CH1 function[7]. Less frequently, AD-DRD presentations may include adult-onset, tremor, and parkinsonism [8]. In the presented case, the patient had AD-DRD with dystonic features starting in childhood and a good response to L-dopa, which is in accordance with what is reported, but she did not present diurnal fluctuation.

Even in L-dopa responders, residual symptoms are not uncommon [9], and these cases may require additional treatments such as anticholinergic medications, dopamine agonists, botulinum toxin injections, or even DBS surgery[10].

Non - motor symptoms such as depression, obsessive-compulsive disorders, and anxiety may also be present, due to monoaminergic deficiency[7]. Available data in DRD patients reveal depressive symptoms in 50%[11], major depression in 34%[12], and anxiety in 19%[12] to 22%[11]. and obsessive-compulsive disorder in 9%[12] to 20%[11], although the existence of a direct pathophysiological association remains controversial[13].

The patient described was diagnosed with recurrent chronic depression, as were her family members, who had the same motor manifestations, which would be related to the non-motor manifestation. DRD may present atypical manifestations beyond the classical phenotype described by Segawa, referred to as DRD-plus, including non-motor symptoms such as psychiatric disorders[7]. The main hypothesis supporting a common substrate is

dysfunction of shared monoaminergic pathways, particularly the dopaminergic and serotonergic systems, with emerging evidence of abnormalities in neurotransmitter levels and their relationships with psychiatric and sleep-related symptoms [14]. Impulsivity may also manifest as a non-motor symptom, possibly related to nigrostriatal dopaminergic hypofunction and the consequent upregulation of D2 dopamine receptors[13].

Otherwise, AR - DRD leads to depletion of dopamine and serotonin, and to severe reduction in tetrahydrobiopterin (BH4).[15] It also causes hyperphenylalaninemia due to impaired conversion of phenylalanine to tyrosine in the liver, resulting from the lack of BH4, a cofactor for the enzyme phenylalanine hydroxylase[9]. AR-DRD presents a more heterogeneous phenotype, including dystonia without parkinsonism, dystonia-parkinsonism, and L-dopa-induced induced dyskinesias[3], [7], and a modest (and sometimes absent) response to L-dopa[15]. Atypical non-motor features such as global developmental delay and cognitive impairment, infantile axial hypotonia, and oculogyric crisis are more frequent in AR-DRD forms and may be the first signs of this form of the disease[3]. When the diagnosis is uncertain but clinical suspicion remains high—particularly in pediatric populations—analysis of cerebrospinal fluid neurotransmitters and metabolites should be considered. In AR-DRD, levels of neopterin, biopterin, 5-hydroxyindoleacetic acid, and homovanilic acid are all reduced in cerebrospinal fluid, whilst phenylalanine may be normal or high in the blood. Also, in AD-DRD, levels of neopterin, biopterin, and 5-hydroxyindoleacetic acid are reduced in cerebrospinal fluid, but the homovanilic acid may be normal [9].

CONCLUSION

The *GCH1* gene, an important cofactor in monoamine synthesis, is associated with several forms of dystonia that range from childhood to adulthood. AD-DRD diagnosis can pose difficulty sometimes, and it should be considered more often. This emphasizes the fundamental importance of a definitive genetic diagnosis for clinical management and genetic counseling. The clinical picture that draws attention, as described in the text, is characterized by dystonia, typically beginning in the lower limbs, with diurnal fluctuation, most often onset in childhood, and an excellent response to L-dopa. It may also have associated non-motor symptoms, which are relevant in this case. So, it is mandatory to consider the diagnosis of DRD in all patients with limb dystonia due to a dramatic response to L-dopa. We reinforce the importance of investigating non-motor manifestations in DRD, as they may be overlooked.

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