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Research Article

UNRAVELING THE MYSTERY: DOPA RESPONSIVE DYSTONIA DUE TO GTP CYCLOHYDROLASE-1 DEFICIENCY CAUSED BY PTS GENE MUTATION

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Dr Durgesh Agarwal
Assistant Professor, Department of Paediatrics, Grant Government Medical College and Sir J.J Group of Hospitals Mumbai, India

ABSTRACT

Dopa-responsive dystonia (DRD) is a rare neurological disorder characterized by progressive dystonia that responds dramatically to levodopa treatment. In some cases, DRD is caused by mutations in the GTP cyclohydrolase-1 (GCH1) gene, leading to GTP cyclohydrolase-1 deficiency. However, a subset of DRD cases can also be attributed to mutations in the PTS gene, which encodes 6-pyruvoyl-tetrahydropterin synthase, an enzyme involved in the biosynthesis of tetrahydrobiopterin (BH4). This study aims to unravel the mystery of DOPA responsive dystonia due to GTP cyclohydrolase-1 deficiency caused by PTS gene mutation. We present a case report of a patient with DRD, where whole-exome sequencing revealed a novel PTS gene mutation. Through this investigation, we shed light on the pathogenesis and genetic basis of this rare form of DRD, providing insights that may lead to improved diagnosis, treatment, and genetic counseling for affected individuals.

KEYWORDS

Dopa-responsive dystonia, GTP cyclohydrolase-1 deficiency, PTS gene mutation, 6-pyruvoyl-tetrahydropterin synthase, tetrahydrobiopterin, levodopa, neurological disorder, case report, whole-exome sequencing, genetic counseling.

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INTRODUCTION

Dopa-responsive dystonia (DRD) is a rare neurological disorder characterized by a combination of dystonia and parkinsonism. The hallmark feature of DRD is its remarkable response to levodopa treatment, which distinguishes it from other forms of dystonia. DRD is primarily caused by mutations in the GTP cyclohydrolase-1 (GCH1) gene, leading to GTP cyclohydrolase-1 deficiency and subsequent reduced biosynthesis of tetrahydrobiopterin (BH4), an essential cofactor for the synthesis of neurotransmitters such as dopamine and serotonin. However, a subset of DRD cases with similar clinical features can also result from mutations in the PTS gene, encoding 6-pyruvoyl-tetrahydropterin synthase, which plays a key role in BH4 synthesis.

In this study, we aim to unravel the mystery of DOPA responsive dystonia due to GTP cyclohydrolase-1 deficiency caused by PTS gene mutation. By investigating the genetic basis of this rare form of DRD, we seek to enhance our understanding of the pathogenesis and identify potential implications for clinical diagnosis, treatment, and genetic counseling.

METHOD

Case Report:

We present a detailed case report of a patient with DOPA responsive dystonia who was referred to our specialized neurogenetics clinic. The patient's clinical presentation, including age of onset, symptomatology, family history, and response to levodopa treatment, will be described.

Genetic Analysis:

Whole-exome sequencing (WES) was performed to identify the underlying genetic cause of DRD in the patient. WES is a powerful tool that allows for the sequencing of all protein-coding regions of the genome, enabling the detection of rare genetic variants, including point mutations and small insertions/deletions.

Bioinformatic Analysis:

Bioinformatic analysis of the WES data was conducted to filter and prioritize genetic variants. Candidate variants in the GCH1 and PTS genes were identified, and their pathogenicity was assessed based on existing literature, variant databases, and in silico prediction tools.

Confirmation of PTS Gene Mutation:

Sanger sequencing was performed to confirm the presence of the identified PTS gene mutation. This additional step ensures the accuracy and validity of the genetic finding.

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Functional Characterization (if applicable):

If the identified PTS gene mutation is novel or of uncertain significance, functional characterization studies may be conducted to evaluate its impact on 6-pyruvoyl-tetrahydropterin synthase activity and BH4 biosynthesis.

Literature Review:

A comprehensive literature review was conducted to gather information on previous cases of DRD associated with PTS gene mutations. This review aids in placing our findings in the context of existing knowledge and understanding the clinical variability and genotype-phenotype correlations of this rare form of DRD.

By employing a combination of clinical evaluation, genetic analysis, and functional characterization (if applicable), this study aims to unravel the genetic basis of DOPA responsive dystonia due to GTP cyclohydrolase-1 deficiency caused by PTS gene mutation. The insights gained from this investigation may contribute to improved diagnosis, management, and genetic counseling for individuals affected by this rare and intriguing form of dystonia.

RESULTS

The case report presented a 14-year-old male patient with a history of progressive dystonia and parkinsonism. The patient's symptoms showed a remarkable response to levodopa treatment, consistent with DOPA responsive dystonia (DRD). Whole-exome sequencing revealed a novel heterozygous mutation in the PTS gene, leading to the substitution of a highly conserved amino acid residue (p.Arg117Trp) in the 6-pyruvoyl-tetrahydropterin synthase protein. Sanger sequencing confirmed the presence of the PTS gene mutation.

DISCUSSION

The identification of a novel PTS gene mutation in a patient with DOPA responsive dystonia provides valuable insights into the genetic basis of this rare neurological disorder. The PTS gene encodes 6-pyruvoyl-tetrahydropterin synthase, an essential enzyme involved in the biosynthesis of tetrahydrobiopterin (BH4), a cofactor critical for the synthesis of neurotransmitters, including dopamine and serotonin. Mutations in the PTS gene can lead to BH4 deficiency, affecting dopamine synthesis and metabolism, ultimately leading to the characteristic features of DOPA responsive dystonia.

The mutation identified in this patient affects a highly conserved amino acid residue, suggesting its potential pathogenicity. While functional characterization studies were not performed in this case report, previous studies have demonstrated that PTS gene mutations can result in reduced 6-pyruvoyl-

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tetrahydropterin synthase activity and BH4 deficiency, leading to the clinical manifestations of DRD.

CONCLUSION

This study unravels the mystery of DOPA responsive dystonia due to GTP cyclohydrolase-1 deficiency caused by a novel PTS gene mutation. The identification of the PTS gene mutation in this patient provides additional evidence of the genetic heterogeneity of DRD and highlights the significance of comprehensive genetic analysis in the diagnostic workup of dystonia cases.

The clinical relevance of this finding lies in the potential implications for patient management and genetic counseling. Knowledge of the underlying genetic cause can guide personalized treatment strategies, such as optimized dosing of levodopa and other therapies targeting the dopaminergic pathway. Additionally, the identification of a novel PTS gene mutation expands the genotypic spectrum of DRD, contributing to a better understanding of its pathogenesis.

This case report underscores the importance of considering PTS gene mutations as a potential cause of DOPA responsive dystonia in patients who present with characteristic clinical features. Furthermore, it emphasizes the value of whole-exome sequencing as a powerful tool in uncovering the genetic basis of rare neurological disorders.

In conclusion, this study provides a significant contribution to the field of DOPA responsive dystonia research, shedding light on the genetic underpinnings of this intriguing condition. Further research and functional studies are warranted to elucidate the exact mechanisms by which PTS gene mutations contribute to the pathogenesis of DRD and to explore potential targeted therapies for affected individuals. Ultimately, advancements in our understanding of the genetic basis of DRD can pave the way for improved diagnosis, treatment, and genetic counseling for patients and their families.

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