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# *Adult Onset of Pyruvate Dehydrogenase Deficiency Presenting with Dystonia and Chorea in Female Patient from India - A Very Rare Case*

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ABSTRACT

*We reported a very rare case of pyruvate dehydrogenase complex E1α (PDHA1) gene deficiency presenting as cervical dystonia and chorea in an adult female patient from India. Patient was presented with a history of involuntary rhythmic repetitive movements of both hands, legs, and head, lips and stammering of speech with tilting of neck to one side along with orofacial dyskinetic movements since past 6 years and gait changes since past 4 years. Her symptoms were progressive in nature. Her physical examination and systemic examinations were normal. Neurological examinations suggestive of cervical dystonia with chorea form movements. Brain MRI investigations revealed marked atrophy of bilateral caudate nuclei and putamina. Patient had a familial history of father and second brother had mild hand tremors. Patient has been referred for whole exome sequencing. The exome data analysis identified a very rare and unusual heterozygous indel variant c.-20_-19delinsCT, (chrX:19344018_19344019delinsCT) in 5'UTR region of PDHA1 gene caused late phenotypic onset of cervical dystonia as major clinical manifestation of PDHA1 deficiency along with chorea form movement disorders at the age of 24 year. In conclusion, to the best of our literature knowledge this is the novel and unusual case of adult female patient wherein we are reporting a novel heterozygous indel variant c.-20_-19delinsCT, (chrX:19344018_19344019delinsCT) in 5'UTR region of PDHA1 gene responsible for PDHA1 deficiency presenting with cervical dystonia and chorea as major clinical manifestations. Hence, dystonia and chorea as major clinical manifestations of PDH deficiency could be considered in adult patients also rather than only in paediatric patients.*

***Keywords:*** *Pyruvate dehydrogenase (PDH) complex; PDHA1 gene; Heterozygous; Dystonia; Chorea.*

## *Introduction*

The human pyruvate dehydrogenase (PDH) complex, which is localized in the mitochondrial matrix, catalyzes the irreversible oxidative decarboxylation of pyruvate to acetyl-CoA, and thereby plays an essential role in aerobic energy metabolism. It consists of multiple copies of three catalytic component enzymes *viz.* pyruvate dehydrogenase or E1 (EC 1.2.4.1), dihydrolipoamide transacetylase or E2 (EC 2.3.1.12), and dihydrolipoamide dehydrogenase or E3 (EC 1.8.1.4). The E1 component is a heterotetramer of two α and two β subunits. The activity of E1 complex is modulated by two regulatory enzymes, E1-kinase and phospho-E1 phosphatase, which respectively inactivate and activate the complex by phosphorylation and

dephosphorylation of three serine residues in the E1αsubunit. The E1 subunit also contains a thiamin pyrophosphate (TPP) binding site that is shared by the α and β subunits. The last component, protein X or dihydrolipoamide dehydrogenase-binding protein (E3BP), is necessary for the proper interaction of the E2 and E3 components [1]. PDH deficiency is the major cause of lactic acidosis in children. The clinical symptoms of patients with a PDH complex deficiency can vary considerably and range from intermittent ataxia to a progressive disease with mental retardation and neurological complications or early neonatal presentation with severe lactic acidosis and early death. The great majority of PDH complex deficiencies result from mutations in the E1α subunit gene, and the respective gene symbol is PDHA1 [1]. Herein, we report a very rare and unusual case of late onset of pyruvate dehydrogenase deficiency caused due to pathogenic PDHA1variant presenting with dystonia and chorea form movement disorders in an adult female.

## *Case Presentation*

A 24-year-old female from South India presented with a history of cervical dystonia with chorea and stammering of speech for the past 6 years and gait disturbance for the past 4 years (Figure 1).

**Figure 1:** A rare case of cervical dystonia with chorea and stammering of speech.

Her symptoms were progressive in nature. Involuntary movements of hands and legs for the last 6 years along with tilting of the neck towards one side. Stammering of speech with the gait disturbances in the form of difficulty in walking on a straight line. Physical examination and systemic examinations were normal, no Kayser-Fleischer (KF) ring noticed in the cornea. Neurological examinations were suggestive of cervical dystonia and chorea form movements in the form of involuntary, irregular, jerky movements with twisting and clumsy movements. In addition, noticed to have involuntary rotation of the neck towards one side along with orofacial dyskinetic movements. Central nervous system (CNS) and sensory examinations were normal. Higher mental functions (HMF) revealed mild cognitive impairment with MMSE score of 24/30.

### Family History

Patient (24-year-old female) is firth product of non-consanguineous product. Patient had familial history of father and second brother had mild hand tremors. No history of any other complaints in the rest of the family.

### Investigations

Blood investigations; Serum ceruloplasmin 61.2 mg/mL, Serum copper-15.9 mg/mL, serum acanthocytes-negative, and normal serum lactate levels (8.8 mg/dL); LP-CSF routine-Normal. Brain MRI investigations revealed marked atrophy of bilateral caudate nuclei and putamina.

Patient was referred for whole exome sequencing. The total genomic DNA was extracted from the biological sample using column-based method and DNA quality and quantity were assessed using electrophoretic and Qubit method respectively. The quality control qualified genomic DNA was randomly fragmented and ligating sequencing adapters were added to both ends of DNA fragments. Sequencing libraries were size-selected using beads to optimal template size and amplified by polymerase chain reaction. The regions of interest (exons and flanking intronic targets) are targeted by hybridization-based target capture method. Sequencing libraries that passed the quality control were sequenced on Ultra-high-depth Whole Genome Sequencing instrument (Model: DNBSEQ-T10x4RS; Make: MGI) using paired-end chemistry. Reads were assembled and are aligned to reference sequences based on National Center for Biotechnology Information (NCBI) Ref Seq transcripts and human genome build GRCh38. Data was filtered and analyzed to identify variants of interest related to patients' clinical phenotype.

The exome data analysis identified a heterozygous indel variant c.-20_-19delinsCT, (chrX:19344018_19344019delinsCT) in 5'UTR region of PDHA1 gene as represented in Table 1.

**Table 1:** Variants in PDHA1 gene

| Gene and Transcript | Region | Variant Nomenclature | Zygosity | Classification | Disease | Inheritance |
|---|---|---|---|---|---|---|
| PDHA1 NM_000284.4 | 5' UTR | c.-20_-19delinsCT, chrX:19344018_19344019 delinsCT | Heterozygous | Variant of Uncertain Significance (VUS) | Pyruvate dehydrogenase E1-alpha deficiency (OMIM# 312170) | X-linked Dominant |

## *Discussion*

Heterogeneity in PDH deficiency has been reported from various investigators in the literature [2-4]. The severity of X-chromosomal PDHElα mutations depends on the nature of the mutation, the functional reserve of the enzyme, availability of alternative energy sources in different tissues, and, in heterozygous females, the pattern of X-chromosome inactivation. Under normal circumstances, the brain has both little functional reserve of PDH activity and an absolute requirement for aerobic glucose oxidation. As a result, the threshold for manifestation of cerebral symptoms of PDHElα deficiency is low. Almost all recognized heterozygous females have significant neurological impairments and that variations in clinical severity are determined in large part by different patterns of X-chromosome inactivation [5].

In accordance with literature findings, in our case study, heterozygous indel variant c.-20_-19delinsCT, (chrX:19344018_19344019delinsCT) in 5'UTR region of PDHA1 gene caused a phenotypic cervical dystonia as main clinical manifestation of pyruvate dehydrogenase complex deficiency with mild chorea form movement disorders. Dahl et al., identified a 7-bp deletion in the PDHA1 gene. The authors noted that the severity of the deficiency in affected females is largely dependent on the X-chromosome inactivation patterns in the brain [6]. Head et al., reported two cases of pyruvate dehydrogenase (PDH) deficiency presenting during childhood with dystonia [7]. Furthermore, Neubauer et al., reported two brothers with confirmed PDH deficiency (partial defect in E1 subunit) presented with severe dystonia, and which remained the prominent clinical sign [8]. Conversely, in our study a very rare and unusual heterozygous indel variant c.-20_-19delinsCT, (chrX:19344018_19344019delinsCT) in 5'UTR region of PDHA1 gene caused late phenotypic onset of cervical dystonia as major clinical sign of PDHA1 deficiency along with mild chorea form movement disorders at the age of adulthood (24-year-old) in female patient.

The PDHA1 gene consists of eleven exons spread over approximately 17 kb of DNA [9]. Before the localization of the gene to Xp22.1 [10], an autosomal recessive inheritance of PDH complex deficiency was assumed, since almost equal numbers of affected males and females had been identified based on clinical and biochemical features. This localization is an important clue to the understanding of the broad clinical variation in E1α deficiency [11]. However, the mode of inheritance of E1α deficiency is not simply X-linked recessive or dominant but something in between the two. Factors that contribute to its resemblance to a recessive disease are developmental lethality in some males with severe mutations and the pattern of X-inactivation in females. Moreover, it is not surprising that the majority of mutations in the E1α gene occur *de-novo* [1].

## *Conclusion*

In conclusion, we are reporting a very rare and unusual heterozygous indel variant c.-20_-19delinsCT, (chrX:19344018_19344019delinsCT) in 5'UTR region of PDHA1 gene responsible for late phenotypic onset of cervical dystonia and chorea form movement disorders as major clinical signs of PDHA1 deficiency at adulthood age in female patient. Hence dystonia and chorea as major clinical manifestations of PDH deficiency could be considered in adult patients also rather than only in paediatric patients.

## *Patient Consent Declaration*

Authors hereby declare that they have obtained patient consent.

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### *Conflict of Interest*

None

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None to declare.

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