Case Report

Perry Syndrome with a Novel Mutation and a Rare Presentation: First Report from India

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Abstract

Objective: To characterize the first patient of Perry syndrome reported from India. Methods: A 62-year-old gentleman presented with acute encephalopathy, hypercapnia, central hypoventilation, and seizures. He required ventilatory support for persistent respiratory failure even after the resolution of the encephalopathy. History revealed symptoms of orthostatic hypotension, episodes of shallow breathing, unsteadiness of gait, anxiety and depression, and significant weight loss for the previous two years. His mother and elder brother had succumbed to a similar illness. Investigations for neuromuscular diseases, including myasthenia and Pompe disease, were negative. Genetic tests for muscular dystrophies and myopathies, investigations for infectious, autoimmune, and para-neoplastic diseases were negative. Neuroimaging and electrophysiological studies were unremarkable. During his hospital stay, he developed rigidity and bradykinesia. Results: In view of the prominent respiratory failure, Parkinsonism, unexplained weight loss, and family history, he was tested for Perry syndrome. A heterozygous missense variation in Exon 2 of the DCTN1 gene that results in the substitution of Proline for Alanine at codon 45 (pA45P) was detected. This variant was not detected in his clinically unaffected brother. The clinical presentation and genetic test indicate Perry syndrome, a rare autosomal dominant fatal disease, which has never been reported from India. The patient improved with Levodopa and neurorehabilitation but eventually succumbed to his illness three years later. Conclusion: Perry syndrome, though rare, should be considered in the differential diagnosis of patients with a family history of Parkinsonism and central hypoventilation.

Keywords: Autosomal dominant, central hypoventilation, DCTN1 gene, Parkinsonism, Perry syndrome, weight loss, genetics

INTRODUCTION

Perry syndrome is a rare familial disorder with onset in late adulthood and characterized by central hypoventilation, Parkinsonism, weight loss and psychiatric symptoms. It is due to a mutation in the DCTN1 gene and is associated with poor survival. We present the first reported case of Perry syndrome from India.

CASE HISTORY

A 62-year-old gentleman presented to us in April 2015 with drowsiness since that morning, followed by generalized tonic-clonic seizures. There was no history of headache, fever, vomiting, or substance abuse. Arterial blood gas analysis revealed hypercarbia (PCO2 >100 mmHg), and he was managed in the intensive care unit with mechanical ventilation. MRI of the brain and cerebrospinal fluid analysis were unremarkable. Electroencephalography showed intermittent generalized slow waves without any epileptiform discharges. Tests for autoimmune and paraneoplastic encephalitis, vasculitis, and Hashimoto’s encephalopathy were negative. The patient’s sensorium improved rapidly within the first 24 hours of admission. Despite the complete recovery of his sensorium and normal limb power, he had difficulty weaning off the ventilator. Therefore, the possibility of a neuromuscular disease was considered. Nerve conduction study, electromyogram, and tests for myasthenia were normal. Serum creatine phosphokinase, ammonia, and lactate levels were normal. A whole-body fluorodeoxyglucose (FDG) positron emission tomography CT scan did not reveal any malignancy, and paraneoplastic antibodies were negative. The patient underwent a tracheostomy and was moved to the ward. Inconsistent left-sided ptosis was noted with restricted extraocular movements, most remarkably, a supranuclear vertical gaze paresis. During his hospital stay, he developed progressively worsening bradykinesia and rigidity but no tremors. No fasciculations or myotonia were evident, and power was normal. Deep tendon reflexes were preserved.

Review of medical history

For three years, the patient had episodes of non-exertional shallow breathing, postural giddiness, and orthostatic hypotension. The cardiac and pulmonary evaluations were

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unremarkable. He also reported a change in his handwriting and mild tremors with fine tasks, mild unsteadiness while turning rapidly, snoring, and mild agitation in sleep. No definite apnoeic spells were noted. He had minor short-term memory errors. He had consulted doctors for ‘depression and anxiety’ but was never prescribed medications. There was no history of the slowness of motor activities, ptosis, diplopia, diurnal variation of symptoms, or fatigability. He had an unintentional weight loss of 7–8 kg over the preceding one year.

**Family history**

There was no history of consanguineous parentage. His mother had a similar respiratory difficulty which developed at 60 years of age, along with excessive daytime somnolence [Figure 1]. She developed altered sensorium prior to her death a few months later. His eldest brother is alive and asymptomatic without any neurological deficits. His second elder brother was admitted to the ICU with respiratory distress and altered sensorium at around 60 years of age and succumbed a few weeks later. He had a similar history of episodes of breathlessness for the preceding two years and reported mild tremors, impaired dexterity of his hands, new-onset snoring, excessive daytime somnolence, lethargy, and mild, subtle short-term memory impairment.

It was evident that he had an autosomal dominant neurological disorder characterized by prominent respiratory involvement, symmetric Parkinsonism with extraocular movement involvement, marked weight loss, mild cognitive and autonomic dysfunction, and mild psychiatric symptoms. Enzyme and a genetic test for Pompe’s disease and Tandem mass spectrometry for metabolic disorders were negative. Muscle biopsy, electron microscopy of muscle, and genetic panel for muscle diseases were normal. Perry syndrome was considered as a possibility, and a genetic test was performed.

**Genetic test**

The patient underwent genetic tests that comprised Muscular Dystrophy (hereditary myopathy with early respiratory failure was one of the differential diagnoses), congenital myopathy, and Parkinson’s disease panels along with the DCTN1 gene. DNA extracted from blood was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to mean > 80–100X coverage on the Illumina sequencing platform. The sequences obtained were aligned to a human reference genome (GRCh37/hg19) using the BWA program and analyzed using the Picard and GATK-Lite toolkit to identify variants in the targeted genes relevant to clinical indication. Clinically relevant mutations were annotated using published variants in literature and a set of variant databases including ClinVar, OMIM, GWAS, HGMD, and SwissVar. A heterozygous missense variation in Exon 2 of the DCTN1 gene with genomic position chr2:74605273; C > C/G and cDNA position c.133G > G/C (ENST00000361874) that

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### Table 1: Diagnostic criteria for Perry syndrome

| Cardinal | Clinical features | Laboratory features |
|----------|-------------------|---------------------|
| A. Parkinsonism | a. Rapid disease progression within five years of onset | 1. Genetic: mutation in the DCTN1 gene. |
| B. Apathy or Depression | b. Onset younger than 50 years. | 2. Pathology: nigral neuronal loss and TDP43 pathology in the brainstem and basal ganglia. |
| C. Respiratory symptoms | D. Unexpected weight loss | |
| E. Family history of Parkinsonism or respiratory symptoms. | |

**Definite:** Presence of (A) and (E) plus positive genetic test (1). Presence of (A), (B), (C), and (D) plus positive genetic test (1). Presence of (A)-(D) plus TDP-43 pathology (2). If evidence of other mutations or neurodegenerative disease pathology is present, there must also be both cardinal laboratory features. Probable: Presence of (A)-(E). Possible: Presence of (A) and (E) plus (a) or (b). (A) Parkinsonism requires two or more among rigidity, tremor (with postural tremor acceptable), bradykinesia, and postural instability. (C) Respiratory symptoms require exclusion of cardiac and pulmonary diseases. TDP-43, TAR DNA-binding protein 43

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**Figure 1:** Family tree of the patient showing autosomal dominant pattern affecting male and female members. 1: Mother: Similar respiratory symptoms. Onset at 60 years of age. Died. 2: Brother 2: Similar respiratory symptoms. Onset around 60 years of age. Died. 3: Patient: 4: Sister 1: Died in the third decade of life. Details are not available. 5: Sister 2: Died due to toxemia of pregnancy. 6: Brother 3: Phenotype of myopathy. Onset at 48 years of age.
results in the amino acid substitution of Proline for Alanine at codon 45 (p.A45P) was detected. The A45P variant is not present in the 1000 genomes database and is predicted to be damaging by SIFT, PolyPhen, and Mutation Taster. This region is conserved across species. This variation was not detected in his elder brother, who was asymptomatic.

**Follow-up**

The patient’s parkinsonian symptoms improved significantly with Levodopa. He was discharged home and continued to recover steadily. His functional status improved markedly, and he remained cognitively stable, ambulant without help, and independent for most of his daily activities. He had mild tremors, bradykinesia, and orthostatic giddiness. He never had a recurrence of seizures. He was confined to home in view of his respiratory insufficiency and required ventilator assistance during sleep. He had repeated episodes of severe respiratory infections and succumbed to one such infective episode in September 2018.

**DISCUSSION**

This patient meets the diagnostic criteria for definite Perry syndrome [Table 1]. The disease was first described in 1975 by Thomas L Perry and remains an extremely rare diagnosis, with only 87 patients described to date and none reported from the Indian subcontinent.[1,2] It is an autosomal dominant neurological disorder characterized by rapidly progressive Parkinsonism, and respiratory failure starting in the fifth decade of life (mean of 49.1 ± 6.6 years) accompanied by varying degrees of psychiatric symptoms, unexplained and prominent weight loss, progressing relentlessly to death in most patients [Table 2].[3] Parkinsonism is usually symmetric, accompanied by tremors that are more often postural than resting, with transient response to Levodopa.[3,4] Our patient had symmetrical rigidity and bradykinesia but minimal tremors. Supranuclear gaze paresis was noted in our patient and is consistent with reports of Perry syndrome presenting with features of progressive supranuclear palsy.[5] Psychiatric symptoms are more frequent than Parkinson’s disease and usually manifest as depression or apathy, which are poorly responsive to therapy.[6] Our patient had minimal psychiatric symptoms and never required medications. Respiratory symptoms are a prominent and diagnostic feature of this disease and eventually require invasive ventilatory support. It is the leading cause of death in Perry syndrome.[7] Polysomnography can identify central hypoventilation and apnoea, which indicates the risk of sudden nocturnal death.[8]

Perry syndrome is due to mutations in the DCNT1 gene encoding a large subunit of the protein Dynactin, with all reported mutations confined to the CAP-Gly domain of Exon 2.[9] Dynactin is essential for intracellular transport, interruption of which leads to cellular dysfunction and intracytoplasmic inclusions. Mutations in the DCTN1 gene have also been reported in distal hereditary motor neuropathy 7B, familial Amyotrophic Lateral Sclerosis, and Fronto-temporal dementia, among others [Table 3].[10,11] Certain mutations like p.G71R are more commonly associated with Parkinsonism, while others like p.F52L may indicate delayed onset of symptoms and a slower progression.[12] Our patient had a p.A45P mutation in Exon 2, which has never been reported before. We propose that this novel mutation may explain the delayed onset of symptoms,

**Table 2: Clinical manifestations of Perry Syndrome**

| **Cardinal signs** | **Uncommon features** |
|--------------------|-----------------------|
| Parkinsonism       | Rigidly, bradykinesia, tremors, impulse control disorders. |
| Psychiatric disturbs | Depression, apathy, hallucinations, suicidal ideation. |
| Unexplained weight loss | Exertional/non-exertional breathlessness. Central hypoventilation |
| Respiratory difficulty | |

**Table 3: Mutations in DCNT1 gene Cap-Gly domain and phenotypes**

| **Mutation** | **Clinical phenotype** |
|--------------|------------------------|
| c.211G>A (p.G71R) | Parkinsonism, hypoventilation, apathy, weight loss, sleep disturbances, mild cognitive impairment. |
| c.233A>G (p.Y78C) | Somnolence, fatigue, mild depression, mild cognitive impairment, apathy, respiratory insufficiency, mild Parkinsonism, weight loss. |
| c.156T>G (p.F52L) | Later onset (48-70 years), long disease duration (2-26 years), Parkinsonism, central hypoventilation, retrocolitis, no depression. |
| c.175G>A (p.G59S) | Lower motor neuron disease without sensory symptoms. The onset of the disease is in early adulthood with breathing difficulty due to vocal cord paralysis, progressive facial weakness, and weakness and muscle atrophy in the hands. Weakness and muscle atrophy in the distal lower extremities develop later. |
| c.175G>C (p.G59R) | Two siblings with identical mutation presenting with different phenotypes, one with features of distal hereditary motor neuropathy and the other with ALS. |
| c.212G>C (p.G71A) | Features of Perry syndrome without hypoventilation or weight loss. Typical features of Perry syndrome. |
| c.200G>A (p.G67D) | |
| c.212G>A (p.G71E) | |
| c.221A>C (p.Q74P) | |
| c.214A>C (p.T72P) | |
| c.202A>G (p.K68E) | Features of Perry syndrome without weight loss. Typical features of Perry syndrome with autonomic features such as urinary and fecal incontinence and paralytic ileus. |
| c.212G>T (p.G71V) | |
prominent respiratory involvement, subtle and delayed parkinsonian features, sustained responsiveness to Levodopa, and negligible psychiatric symptoms. This contrasts with the descriptions recorded in literature where the most common initial symptom was depression/apathy (71.4% of patients) followed by weight loss (49.2%) and Parkinsonism (95.2%) and lastly, respiratory difficulty (66.7%), with sudden death occurring in 15.2% of patients.

**Conclusion**

Though rare, Perry syndrome should be considered as a diagnostic possibility in the context of familial Parkinsonism with respiratory involvement. Finding novel mutations associated with the syndrome could explain the varying clinical presentations of this disorder and aid in the diagnostic processes.

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**Conflicts of interest**

There are no conflicts of interest.

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