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Latin America's first case of Perry syndrome and a new treatment option for respiratory insufficiency

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Dear Sirs,

Perry syndrome is an autosomal dominant disorder characterized by rapidly progressive Parkinsonism, depression, weight loss, and central hypoventilation [1]. Since the original publication in 1975, only 52 patients from ten families have been found, but no case had been reported from Latin America. The mean age of symptom onset is 48 years, and the mean disease duration is 5 years. Patients usually die of respiratory complications. Genome-wide linkage analysis identified disease-segregating mutations located in exon 2 of the dynactin 1 (*DCTN1*) gene on chromosome 2p13 [4].

A 56-year-old Colombian female was admitted to the Hospital Universitario San Ignacio, in Bogotá, Colombia, with acute deterioration of her respiration. On clinical examination, the patient displayed generalized anxiety and a severe depressive episode. She reported a weight loss of 15 kg in 6 months. The patient had a 2-year history of Parkinsonism, which comprised hypomimia, cogwheel rigidity in all extremities, and low-frequency postural and intention tremor of the upper extremities that was more pronounced on the left side.

Levodopa at a maximum daily dosage of 1,000 mg combined with 100 mg of carbidopa slightly improved the tremor. Brain MRI, EEG, and muscle biopsy did not show any relevant abnormalities. A gas blood analysis on admission showed the following values: FiO_2 21 %, pH 7.32, pCO_2 60 mmHg, PO_2 20 mmHg, HCO_3 31 mmol/l, $SatO_2$ 88 % with a supply of 2 l of O_2 per minute via nasal cannula. This demonstrated severe respiratory acidosis with acidemia. There was no history of chronic obstructive pulmonary disease. The

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patient's body max index was 16.6. Diagnostic procedures to clarify the etiology of the respiratory insufficiency included diaphragm electromyography (EMG), the mouth pressure generated 100 ms after the onset of an occluded inspiratory effort (P0.1), and the transdiaphragmatic pressure (Pdi) measured with a transesophageal probe. Their results were as follows: normal EMG, 9 cm H_2O (P0.1), and 5 cm H_2O (Pdi), which suggested a central etiology.

Due to unstable and deteriorating respiratory conditions, no polysomnography could be performed. Instead, the patient was placed on mechanical ventilation following tracheostomy. Numerous attempts to treat her with noninvasive respiratory support over a period of 2 months prior to the hospital admission had been unsuccessful. Efforts to wean the patient off a ventilator during other 2 months following the admission failed. Thus, the patient was fitted with a bilateral diaphragmatic pacemaker with direct stimulation of the phrenic nerve (Mark IV Breathing Pacemaker System, Avery Biomedical Devices, Inc.) following a bilateral anterior thoracotomy with a 6-cm transverse incision over the third intercostal space. The surgery was complicated by a mild right hematothorax and subcutaneous emphysema. The patient was stimulated with a pulse train of 20 Hz. The most common pacemaker settings were an amplitude of 1.6 mA and a respiratory frequency of 15 breaths per minute. Two-year-follow-up examinations have displayed a good function of the diaphragmatic pacemaker. The patient became independent in her everyday life. There have been no episodes of acute respiratory failure, albeit the patient has occasionally developed pneumonia. This has successfully been treated with antibiotics. Implantation of a diaphragmatic pacemaker also enabled to avoid the very high costs of permanent ventilatory support.

Family history revealed the same symptoms in her mother and another nine relatives on her mother's side, including four uncles, two sisters, and three cousins. All died of respiratory insufficiency. Molecular genetic testing for Perry syndrome confirmed this diagnosis revealing the c.211 G > A (p.G71R) mutation in exon 2 of the DCTN1 gene on chromosome 2p13.1.

Our patient is Latin America's first genetically confirmed case of Perry syndrome. Contrary to other cases, our patient presented with mild extrapyramidal symptoms and pronounced respiratory insufficiency as the main complaint. However, the latter has successfully been treated with the use of a diaphragmatic pacemaker.

Our case is the first successful attempt to apply a diaphragmatic pacemaker in a patient with Perry syndrome, although diaphragmatic pacemakers in the form of direct phrenic nerve pacing (Diaphragmatic/Phrenic Nerve Stimulator) have already been applied in the symptomatic treatment of different conditions such as congenital central hypoventilation syndrome [5] or medullary trauma [6]. Diaphragmatic pacemakers with the direct stimulation of the diaphragm (Diaphragm Pacing Systems) have been approved by the US Food and Drug Administration in the treatment of ventilator failure in amyotrophic lateral sclerosis [7], spinal cord injuries, and congenital central hypoventilation syndrome.

We conclude that implantation of a diaphragmatic pacemaker should be considered as a safe, effective, and cost-reducing treatment option for respiratory insufficiency in patients with Perry syndrome. Early diagnosis significantly improves the patient's quality of life and prevents life-threatening acute respiratory failure. Parkinsonian features, although always present in Perry syndrome, may not be disabling in some cases. Perry syndrome is not geographically constrained. New cases from South America are expected to be diagnosed.

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Ethical standard This study was approved by the Institutional Review Boards of Pontificia Universidad Javeriana, Bogotá, Colombia and the Mayo Clinic and was therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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