Congenital Central Hypoventilation Syndrome: The Singularity of A Successful Case

Síndrome de Hipoventilação Central Congénita: A Propósito de Um Caso de Sucesso

Keywords: Hypoventilation/congenital; Infant; Infant, Newborn; Sleep Apnea, Central/genetics
Palavras-chave: Apneia do Sono Tipo Central/congénita; Hipoventilação/congénita; Lactente; Recém-Nascido

Dear Editor,

Congenital central hypoventilation syndrome (CCHS) is a rare autosomal dominant genetic disease, with an estimated incidence of 1 per 148 000 – 200 000 live births,[1] caused by a mutation in the paired-like homeobox 2B (*PHOX2B*) gene encoding a transcription factor that is critical for the development of the autonomic nervous system. It is characterized by autonomic failure, with absence or decreased sensitivity to hypercapnia and hypoxemia, especially during sleep, causing hypoventilation and apneas. The diagnosis of CCHS should be made in the presence of sleep-related hypoventilation [especially in non-rapid eye movement (NREM) sleep] and *PHOX2B* mutation.[2] The longer polyalanine repeat expansion mutations (PARMs) typically present a classic phenotype, usually with the need for continuous ventilatory support and the onset of symptoms in the neonatal period. If accurate diagnosis and organ support are assured, CCHS is a chronic disease compatible with life, allowing patients to reach adulthood. Ventilatory support is the cornerstone of treatment.[3]

A 22-year-old woman was born from pre-term labor at 32 weeks, with generalized hypotonia, symptomatic central apneas, and ineffective ventilation, with the need for invasive mechanical ventilation (IMV) to be started during the neonatal period. There were no family members with similar manifestations. A CCHS diagnosis was established at two months, after the exclusion of other diseases, before *PHOX2B* genetic testing was available. Once diagnostic confirmation was possible, the presence of a PARM 20/27 was documented. The patient acquired an adequate ventilatory capacity during wakefulness at 10 months, and transition from IMV to non-invasive ventilation (NIV) was possible at 10 years. She reached adulthood with normal motor and cognitive development (Fig. 1). The parents were also tested and are not gene mutation carriers.

Invasive mechanical ventilation is the most frequent type of ventilatory support and is recommended until the ages of six to eight years through tracheostomy.[3] The use of NIV, especially if performed only during sleep, allows for an almost normal childhood and improved quality of life.[4] In this case, the acquisition of adequate ventilatory capacity during wakefulness is noteworthy. This is seldom described in the literature, mainly by the age of six to 12 months, being more frequent in patients with shorter PARMs.[2] Although the transition from IMV to NIV might impact the correction of alveolar hypoventilation, this case emphasizes that it is a safe and effective treatment, as demonstrated by the absence of polycythemia, pulmonary hypertension, *cor pulmonale*, or cognitive deficits. It is not clear whether neurological deficits are a primary manifestation of the disease or the result of untreated chronic hypoxemia.[5]

The authors emphasize the singularity of this case, in which the diagnosis was established in the pre-*PHOX2B* genetic testing era. It is also of note the ventilatory autonomy achieved during wakefulness at the age of 10 months in a patient with long PARM, and her normal motor and cognitive development.

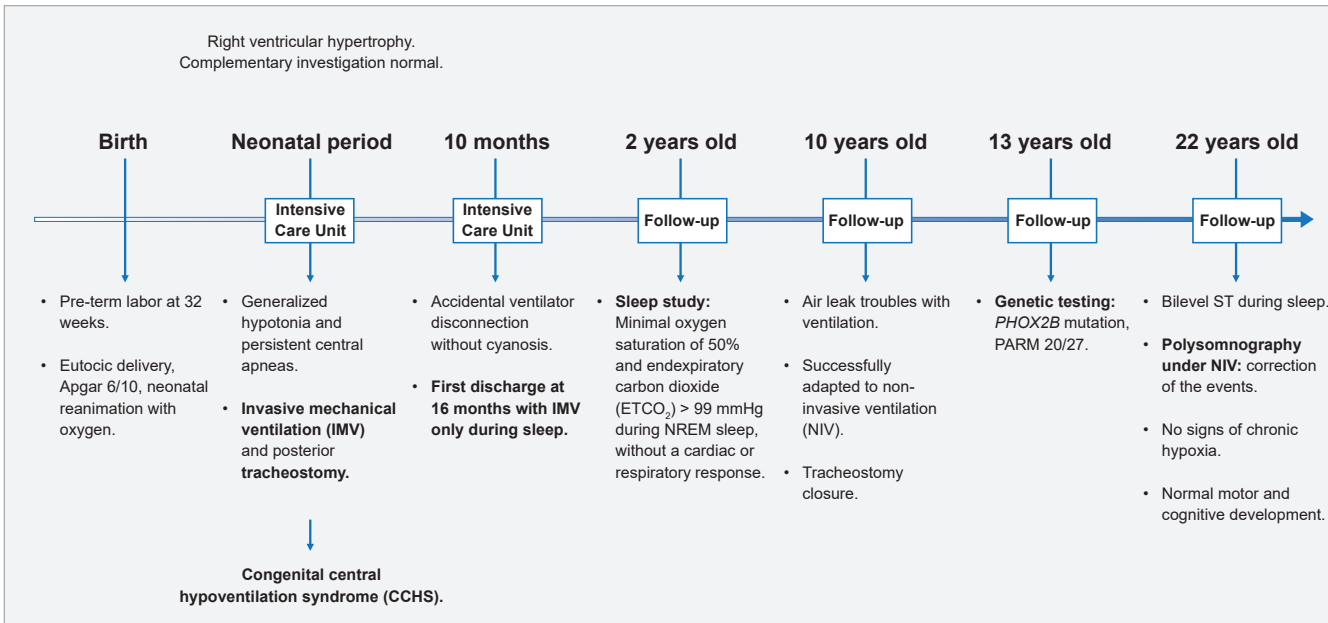

Figure 1 – Timeline highlighting the patient's clinical presentation and most relevant complementary exam findings

AUTHOR CONTRIBUTIONS

IB, IFP, DA: Literature review and writing of the manuscript.

MLP, SM: Writing and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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REFERENCES

1. Trang H, Samuels M, Ceccherini I, Frerick M, Garcia-Teresa MA, Peters J, et al. Guidelines for diagnosis and management of congenital central hypoventilation syndrome. Orphanet J Rare Dis. 2020;15:252.
2. Darien IL. International classification of sleep disorders. 3rd ed. Illinois: American Academy of Sleep Medicine; 2014.
3. Weese-Mayer D, Berry-Kravis E, Ceccherini I, Keens TG, Loghmanee DA, Trang H, et al. An official ATS clinical policy statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. Am J Respir Crit Care Med. 2010;181:626-44.
4. Kam K, Bjornson C, Mitchell I. Congenital central hypoventilation syndrome; Safety of early transition to non-invasive ventilation. Pediatr Pulmonol. 2014;49:410-3.
5. Charnay A, Antisdel-Lomaglio J, Zelko F, Rand CM, Le M, Gordon SC, et al. Congenital central hypoventilation syndrome neurocognition already reduced in preschool-aged children. Chest. 2016;149;809-15.

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