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CLINICAL CASE

Congenital Central Hypoventilation Syndrome: neonatal diagnosis and management

Síndrome de Hipoventilación Central Congénito: diagnóstico y manejo neonatal

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What do we know about the subject matter of this study?

Congenital central hypoventilation syndrome (CCHS) is a rare, autosomal dominant pathology. It is confirmed by sequencing the PHOX2B gene. Its severity is variable, depending on the number of repeats, with clinical presentation as sudden death and central hypoventilation, with the need for partial or total invasive mechanical ventilation (IMV). The discharge process becomes difficult due to the requirement of a tracheostomy for prolonged IMV. Neonatal confirmation allows early comprehensive management of a potentially lethal disease.

What does this study contribute to what is already known?

In the neonatal presentation with central hypoventilation during sleep, it is possible to avoid tracheostomy and establish noninvasive ventilatory support (NVS), with good general and psychomotor development.

Abstract

Congenital Central Hypoventilation Syndrome (CCHS) is a rare genetic condition affecting the autonomic nervous system and respiratory center due to mutations in the PHOX2B gene, and it is associated with alveolar hypoventilation during sleep and sudden death. It requires early invasive mechanical ventilation (IMV). **Objective:** To report a neonatal case successfully treated with non-invasive ventilatory support (NVS), avoiding tracheostomy. **Clinical Case:** Full-term newborn, whose mother

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uses nocturnal NVS due to CCHS. During the transition period, she presented desaturations associated with hypercapnia and respiratory acidosis, without pulmonary involvement. She developed severe hypoventilation during sleep, with no respiratory effort, peripheral oxygen saturation (SpO2) < 80%, plus respiratory acidosis. While awake, she had good respiratory effort and normal SpO2 without assistance. Noninvasive continuous positive airway pressure and oxygen therapy worsened her condition while sleeping. Complete NVS with nasal interface and bi-level airway positive pressure, inspiratory/expiratory pressure 14-16/4 cm H2O, normalized SpO2 during sleep, and arterial blood gases while awake. Sequencing of the PHOX2B gene confirmed the presence of a heterozygous pathogenic variant with the 20/26 genotype. At 2 months of age, she was discharged maintaining NVS with nasal interface and 0 PEEP, achieving adequate neurodevelopment. **Conclusion:** We highlight the importance of genetic diagnosis of CCHS in neonates with clinical presentation of early alveolar hypoventilation, especially if there is a family history. We are not aware of other reports of neonatal onset in which NVS prevents IMV, in this potentially lethal pathology.

Introduction

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder of the autonomic nervous system with an estimated incidence of 1 in 200,000 live births[1]. It is caused by variants in the homeobox 2B (PHOX2B) gene on chromosome 4p13 which, under normal conditions, contains a 20-alanine repeat sequence in exon 3[2]. The number of repeats in this sequence is associated with severity, which conditions the compromise of the respiratory center and ventilatory autonomy. The higher the number of repeats, the more likely the need for complete ventilatory support night and day, especially in children under 6 years of age[3].

The PHOX2B gene mutation has an autosomal dominant inheritance with variable penetrance. In 90% of cases, it occurs through a *de novo* mutation, and in the remaining 10% it is due to germline mosaicism with or without somatic mosaicism[3].

The homeobox transcription factors are necessary for the embryogenesis of the neural crest and the autonomic nervous system, being expressed in central and peripheral noradrenergic neurons, parasympathetic and sympathetic ganglia, visceral and branchial motor neurons, as well as primary and secondary visceral sensory neurons[4]. Therefore, alterations in the PHOX2B gene can simultaneously alter the development of the central and peripheral nervous system, frequently presenting an association of CCHS with Hirschsprung's disease, alterations in heart rate, blood pressure, body temperature, hormonal regulation, and pupillary response[5-7].

The onset in patients with CCHS may occur at any stage of the life cycle, but generally, those presenting in the neonatal period have altered respiratory center control and lack normal responses to hypoxemia and hypercapnia. This results in a variety of clinical manifestations, including apnea, hypoxemia, and hypoventilation, which manifest predominantly during sleep and, in some cases, may persist even during wakefulness[8].

Normally, children during transitional sleep maintain good control of the respiratory center with proper integration of metabolic afferents and CO_2 partial pressure. However, in this pathology, these afferents are not read, preventing the generation of the respiratory drive[7,8] and by lacking objective and subjective responses to hypoxemia and hypoventilation, they do not manifest signs of respiratory distress such as nasal flaring, tachypnea, and intercostal retractions[9].

In these patients, the use of oxygen therapy, not associated with respiratory pump support, exacerbates hypercapnia and respiratory acidosis[9], which may cause lethality. This fact is extremely complex since the causes of hypoxemia in neonates and infants are generally due to cardiorespiratory causes with a high prevalence of parenchymal lung diseases.

To maintain adequate oxygen saturation ranges and normal PCO_2 levels, all patients with CCHS will require different ventilatory support modalities[10].

The objective of this article is to report the successful management of a neonate with CCHS using noninvasive nasal ventilatory support (NVS), thus avoiding prolonged invasive mechanical ventilation (IMV) by tracheostomy and therefore more complex hospitalization processes and facilities.

Clinical Case

Term newborn, 38 weeks of gestational age, born via planned cesarean section, Apgar 8-8, birth weight 2,895 g, length 47 cm, head circumference 34 cm, and normal thoracic circumference.

As a relevant family history, her 29-year-old mother was diagnosed with CCHS, requiring mechanical ventilation through tracheostomy from the age of 2

years and later NIV with nasal interface and adjusted positive pressure throughout her life. Since her condition was not associated with ventilatory control defect during wakefulness, delivery was resolved vaginally without complications.

During the neonatal transition period, the newborn presented frequent desaturations. Arterial blood gases showed hypercapnia ($PaCO_2$ 60-80 mmHg) and respiratory acidosis (pH < 7.20 with base excess of 8-10). The rest of the internal parameters were normal.

She was admitted to the neonatal intensive care unit of the *Hospital Clínico San Borja Arriarán*, where a normal respiratory pattern and pulse oximetry (SpO2) > 95% were observed in wakefulness, with mild central hypotonia and progressive improvement to normal tone. During the transition from wakefulness to sleep, she presented very shallow breathing, not associated with increased work of breathing, wheezing or stridor, with progressive desaturation (SpO_2 < 85%), which worsened with oxygen administration without NIV, with blood gases through an umbilical catheter in the range previously described. As sleep deepened, SpO_2 tended to stabilize between 85-90% with continuous positive airway pressure (CPAP) using positive end-expiratory pressure (PEEP) 6-7 cmH20 administered with nasal mask alternating with short binasal prong, without normalizing arterial blood gases.

At 36 hours of life, support was changed from cycled CPAP to NVS modality, using peak inspiratory pressure (PIP) of 14-16 cm H_2O and PEEP of 4 cm H_2O, using only nasal mask interface, normalizing oxygenation during sleep and blood gases during sleep and wakefulness.

Given the high suspicion of CCHS, the PHOX2B gene sequencing was performed, confirming a heterozygous pathogenic variant with genotype 20/26 at 7 days of life. The study was completed with cranial ultrasound, echocardiogram, and 24-hour Holter monitoring, all normal. The need for specialized sleep studies was dismissed given the confirmed diagnosis and the urgent requirement for complete NVS during sleep. She was evaluated by a multidisciplinary team including cardiologists, neurologist specialists for sleep disorders, pulmonologists, speech therapists, pediatricians, and home hospitalization kinesiologists with expertise in prolonged NVS.

After one month of life, the patient was transferred to a unit of lesser complexity to maintain NVS during full sleep, i.e., with adequate positive pressure to allow complete normalization of noninvasive monitoring of the SpO_2 line > 90% at sleep, and complete normalization of blood gases in wakefulness including baseline excess. The Philips™ Trilogy EVO hybrid home ventilator with a single-limb circuit and external exhalation valve was used to deliver PEEP = 0 cm H_2O and a positive pressure of 14-16 cm H_2O, in Assist Control (Pressure Control) (A/C-PC) mode with respiratory rates of 30 per minute and inspiratory time of 0.7 seconds.

She presented a satisfactory evolution, without complications, and was discharged to home hospitalization with the same nasal NVS program only when sleeping. At 7 months of life, clinically normal psychomotor and neurocognitive development was evident, without requiring hospitalization for any type of event.

Discussion

This clinical case presents relevant information on the use of NVS in a patient with neonatal onset of CCHS, diagnosed based on maternal history and compatible genetic study. We were able to avoid the use of IMV and tracheostomy to establish prolonged mechanical ventilation, which is usually indicated as soon as technically possible in these cases[11].

90% of CCHS cases are caused by variants with expansion of the normal 20-repeat alanine sequence to 24-33 repeats, producing genotypes from 20/24 to 20/33[1]. In this patient, confirmation of 6 alanine repeats is typically associated with the need for partial IMV during sleep[12].

Other manifestations of neural crest cell-derived multiorgan dysregulation, such as Hirschsprung's disease and cardiovascular alterations, have not been observed in the follow-up of this case[13], possibly because they are linked to less common variants with more severe phenotypes requiring prolonged mechanical ventilation. However, long-term follow-up will require actively ruling out autonomic nervous system disorders and late manifestations of neurocristopathies[3-13].

Hypoventilation of other origin, such as structural and acquired pathology of the central nervous system, upper airway obstruction, and pulmonary parenchymal involvement were ruled out before genetic confirmation. The early availability of this study made it possible to avoid specialized sleep studies, such as polysomnography, to verify hypoventilation during sleep, the lack of response to hypercapnia, and the worsening with oxygen therapy, characteristic of this condition[14,15]. In addition, correction of hypoventilation with NVS prevented the withdrawal of support to confirm these disorders.

The noninvasive ventilatory strategy, defined as complete NVS, differs from the usual noninvasive mechanical ventilation strategies, which use low positive pressures (≤ 10 cmH_2O), increased PEEP, or limitation of ventilation volumes as if the primary alteration was pulmonary and not central. This definition of NVS is used to avoid tracheostomy in patients with alveolar hypoventilation secondary to neuromuscular diseases

(NMD), including those with very early onset, such as spinal muscular atrophy type 1[16-18]. Likely, this strategy was so well suited to the needs of this patient by correcting alveolar hypoventilation due to primary respiratory drive defect, which in NMD is caused by hypercapnia and respiratory pump failure.

The goal of NVS was to achieve normal oxygenation ($SpO_2 \geq 95\%$) and normocapnia (PCO_2 35-45 mmHg), in the same manner as has been described with traditional ventilation management with invasive interfaces[15-17]. In this patient, there was a change from a bi-level setup with a passive circuit to an active circuit with external expiratory valve, PEEP = 0 cmH_2O, optimizing the positive pressure and minimizing unintentional leaks, using A/C-PC mode. Likely, titration using noninvasive trend tests such as oxycapnography would better correct hypoventilation. Unfortunately, this resource was not available, so we resorted to sleep SpO_2 and blood gas trend studies.

It is noteworthy that this patient has been maintained exclusively with NVS during sleep, unlike what usually occurs in CCHS, where assisted ventilation is required throughout the day or only at night, generally until the age of 6 years through a tracheostomy[19]. At this age, some patients may benefit from diaphragmatic pacing, but without necessarily being able to be decannulated, and those of lesser severity may transition to nocturnal-only noninvasive ventilation[20].

In patients managed with IMV, the risks associated with a tracheostomy cannula are high and related to accidental disconnection, obstruction, decannulation, pneumonia, and airway injury. These patients have a high level of dependency and early hospital discharge is unlikely. In our case, the clinical progress has shown that NVS was effective and efficient, allowing home management, with supervision by a specialized home hospitalization unit of the public system, where direct care is provided by the mother, also a NVS user.

Some infants with neonatal CCHS have received mask ventilation without tracheostomy. Migliori published his experience in the management of 2 infants who started NVS at 53 and 31 days, and successfully ventilated with a bi-level positive-pressure device with nasal interface[21]. Paglietti et al. reported the case of an infant with a history of Hirschsprung's disease and apneas, confirmed by genetic study of CCHS and successfully managed with SVN[22]. Tibballs et al. reported another case of a neonate with confirmed genetic diagnosis, extubated at 6 weeks of life to mask and bi-level ventilation, achieving $PaCO_2$ of 40-55 mmHg, without describing the setup[23]. These differ from this study where the use of full NVS setup started successfully from the first week of life.

Conclusion

We present a case of a neonate carrier of genetically confirmed CCHS, in which the use of NVS during sleep in a complete setup proved to be effective in avoiding the need for IMV, allowing a satisfactory development. Early management by interdisciplinary teams can facilitate the transition to home in this rare, life-threatening pathology with a high health burden.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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