

ORIGINAL ARTICLE

Congenital central hypoventilation syndrome – heterogeneous clinical presentation, ventilatory modalities and outcome

Mihail Basa¹, Jelena Visekruna¹, Bojana Gojsina Parezanovic¹, Tijana Grba¹, Marina Andjelkovic³, ✉ Aleksandar Sovtic^{1,2}

Department of Pulmonology, Institute for Mother and Child Health Care of Serbia, Belgrade, Serbia

University of Belgrade, Faculty of Medicine, Belgrade, Serbia

Laboratory for Molecular Biomedicine, Institute of Molecular Genetics and Genetic Engineering, Belgrade, Serbia

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✉ Correspondence to:

Aleksandar Sovtic

Department of Pulmonology, Mother and Child Health Care Institute of Serbia,

6-8, Radoja Dakica Street, 11070 Belgrade, Serbia

Telephone: +381113108158

Email: aleksandar.sovtic@med.bg.ac.rs

Summary

Introduction/aim: Central congenital hypoventilation syndrome (CCHS) is a rare genetic disorder characterized by autonomic dysregulation and alveolar hypoventilation with ventilatory support being the cornerstone of long-term survival. The aim was to present different ventilatory strategies in CCHS.

Material and methods: The study included retrospectively analyzed medical records of five patients diagnosed with CCHS in a national pediatric center. Alveolar hypoventilation was evidenced by noninvasive continuous transcutaneous capnometry and central sleep-disordered breathing documented by polygraphy. Clinical evaluation included cardiac evaluation, rectal biopsies, and urinalysis of catecholamine levels. Life-threatening cardiac arrhythmias were indications for pacemaker implantation. Genetic analyses of alanine residues in paired-like homeobox 2B gene (*PHOX2B*) confirmed the diagnosis.

Results: A range of pathogenic changes in the *PHOX2B* gene resulted in varying clinical outcomes. 3/4 (75%) of patients with an early onset were ventilated continuously through a tracheostomy tube, while one patient was successfully treated with noninvasive ventilation (NIV) as the preferred option. Additionally, NIV was applied in one child with early-onset disease after decannulation. Finally, NIV was also feasible in a case with late-onset disease presented by the time of four years with symptoms of pulmonary hypertension. There were no serious side effects of ventilation, and one patient died due to cardiac arrhythmias.

Conclusion: Invasive mechanical ventilation remains the treatment of choice in most children with early-onset disease. However, the indications for NIV have been widened from overnight ventilation in the late-onset course to selected cases with early-onset disease. The timely switch from IMV to NIV has been popularized in recent years worldwide.

Key words: central congenital hypoventilation, invasive ventilation, noninvasive ventilation, decannulation

INTRODUCTION

Central congenital hypoventilation syndrome (CCHS) is a rare incurable genetic disorder characterized by heterogeneous clinical patterns, respiratory and autonomic dysregulation being the main clinical concern (1). It has been estimated that there are about 1300 cases of CCHS worldwide with an estimated incidence of 1/148.000-1/200.000 live births (1). Most frequently (90% cases), it is caused by polyalanine repeat expansion mutation (PARM) of paired-like homeobox 2B (PHOX2B) gene located on chromosome 4 and expressed in the cells of the neural crest where it has an important role in cellular migration and differentiation. Former and latter processes are essential for the development of all respiratory and vasomotor centers and autonomic nervous system (ANS) functions (2). Thus, the heterogeneous clinical expression of CCHS is explained simply by autonomic functions of ANS in which PHOX2B takes participation: breathing, heart rate, blood pressure, body temperature, hormonal regulation, digestive function, and pupillary reactivity (3). Very few children (up to 10%) have a non-PARM genotype (NPARM) resulting from a missense, nonsense, frameshift, or stop codon mutation. CCHS is inherited in an autosomal dominant manner and mainly occurs via de novo mutations, while a small proportion of cases show germline mosaicism with/without somatic mosaicism (4).

Typically, diurnal hypoventilation with diminished respiratory drive and cyanosis in response to hypercarbia is manifested during infancy (5,6). Rarely, a proportion of children tend to have milder phenotypes with only nocturnal hypoventilation (5,6). However, both forms are often coupled with symptoms of autonomic dysregulation: cardiac (cardiac arrhythmias), intestinal (congenital megacolon, i.e. Hirschsprung disease), ocular symptoms (mostly pupilar abnormalities), and tumors of neural crest origin (neuroblastoma and ganglioneuroma) (7–10). Genotype-phenotype association shows a positive correlation between both the length of polyalanine string and non-polyalanine repeat expansion alterations and severity of the disease (11,12).

Though ANS disorders and tumors impose significant healthcare challenges with a potential to increase mortality rates, treatment of respiratory insufficiency still remains the cornerstone of long-term survival (13,14). While chronic invasive mechanical ventilation (IMV) represents a traditional treatment modality, the importance of noninvasive ventilation (NIV) has been popularized and highlighted in recent years in selected patients, e.g., after decannulation or in those with late-onset disease (14-16). With better overall medical care directed at each aspect of the disease, the field of indications for NIV has become wider in the past decade (14–16).

We intended to present the experiences of the leading national pediatric respiratory center treating patients di-

agnosed with CCHS with special emphasis on long-term ventilatory support. The important goal was to underline the criteria for a timely switch from invasive chronic mechanical ventilation to NIV.

MATERIAL AND METHODS

The study includes retrospectively analyzed medical records of five patients diagnosed with CCHS from 2008 to 2022 in the Department of Pulmonology of the Institute for Mother and Child Health Care of Serbia, the national center for home mechanical ventilation in children.

Criteria for diagnosis

Referrals for genetic testing were made for patients in whom sleep study results had revealed central pattern and chronic alveolar hypoventilation and who showed blunted response to hypercarbia and hypoxemia – either as an absence of respiratory drive or multiple failures to wean from mechanical ventilation without specific explanation. Additionally, the possibility of hypoventilation was considered in patients with idiopathic pulmonary hypertension, sleep disordered breathing, and signs of autonomic dysfunction. Diagnosis of CCHS was based on the number of sequence repeats in the *PHOX2B* gene.

Genetic testing

Having extracted DNA from peripheral blood, PCR analysis of the exon 3 of *PHOX2B* gene coding for the CCHS-associated polyalanine repeat sequence expansion was performed using primers flanking specific regions. The number of alanine repeats was quantified via gel electrophoresis of the PCR product and compared with standard alleles typically containing 20 repeats. CCHS-confirmative findings were those containing 25–33 alanine repeats. Genetic counseling for family members was recommended in each confirmed case.

Respiratory evaluation

Hypercarbia was detected by spot arterial blood gas analyses (ABG) and/or noninvasive continuous transcutaneous capnometry (PtcCO₂) results. More than 2% of the total sleep time (TST) with PtcCO₂ > 50 mmHg was indicative of nocturnal hypoventilation (17,18). Sleep study (polygraphy) was performed simultaneously in all patients, when possible, except in patients chronically ventilated in ICU. Respiratory events were scored by two experienced physicians according to the American Academy of Sleep Medicine (AASM) (19). Flexible bronchoscopy was performed in each patient to evaluate possible structural anomalies of the airways.

Modes of ventilatory support

The onset of ARF and daily requirements for respiratory support further defined treatment strategies in subjects diagnosed with CCHS. Patients who had experienced ARF in infancy with a permanent (>16 hours a day) need for ventilatory support were considered to have an early-onset disease. They were tracheostomized, and the treatment of choice was chronic invasive mechanical ventilation with pressure-control mode. A specific protocol for decannulation was used, as described elsewhere (20). Patients diagnosed with CCHS that presented only with nocturnal hypoventilation and preserved bulbar function without neurodevelopmental delay were primarily ventilated noninvasively via nasal or full-face masks.

Prior to discharge, parents/caregivers were trained to provide satisfactory, all-day-long medical care to the children including tracheal suctioning with cough assist device usage, tube feeding when needed, and training related to basic ventilatory settings and alarms. Once discharged, patients were mechanically ventilated at home.

Efficacy of the respiratory support in each patient was evaluated regularly in three-month intervals using ABG, continuous transcutaneous capnometry, and in-built software data from the memory cards of the ventilators.

Evaluation of the autonomic nervous system

Both echocardiography and heart rhythm disturbances evaluation were part of routine workup. Life-threatening arrhythmias were indicators for pacemaker implantation. Regular cardiac reevaluation was mandatory at least twice a year as a part of follow-up.

Regular ophthalmologic evaluation was also provided from initial admission onward, at least annually. Each patient was screened for neural crest tumors with vanilmandelic (VMA) and homovanilic (HVA) blood and urinalysis.

Unlike the aforementioned, congenital megacolon screening was not routinely included. It was conducted only when necessary – in selected patients with symptoms of intestinal obstruction. Those with mild intermittent symptoms of intestinal obstruction underwent transanal

rectal biopsy, while abdominal X-ray and urgent surgery were opted for in patients with a severe acute presentation. Postcolectomy pathohistological verification of the absence of intramural ganglion cells was mandatory.

Thorough neurologic and metabolic workup was undertaken in each case to diagnose disorders that included hypoventilation as a secondary phenomenon.

RESULTS

The study included five patients diagnosed with CCHS all of whom were females aged from birth to four years. Clinical presentation, including the onset and severity of the disease correlated with genotype: those with the early-onset disease had 27 alanine residues in exon 3 of the *PHOX2B* gene, while one child with the late-onset disease had 25 alanine repeats. The main clinical and genetic features are given in **Table 1**.

A range of pathogenic changes in the *PHOX2B* gene resulted in varying degrees of cellular dysfunction, thereby influencing the phenotype of an individual patient with CCHS. Most of the patients with genotype 20/27 required continuous ventilatory support and had clinical manifestations of autonomic dysfunction including Hirschsprung disease - as seen in three out of four analyzed patients with 20/27 PARM *PHOX2B* genetic alteration (Table 1 and Table 2). In those three cases, long-term mechanical ventilation was applied through a tracheostomy tube. The mean age at tracheostomy tube insertion was three months. None of the patients had structural airway abnormalities on flexible bronchoscopy.

A milder disease course and an absence of Hirschsprung disease were confirmed in the analyzed patient harboring the 20/25 PARM *PHOX2B* genetic alteration (**Table 1 and Table 2**) and presented with late-onset disease and symptoms of pulmonary hypertension. NIV turned out to be feasible in this child. Furthermore, NIV was also used as a definite treatment option in one case with 20/27 genotype with early-onset disease after a successful extubation in the first postnatal week, as well as in one child after decannulation at the age of six.

Table 1. The main clinical and genetic features in patients with CCHS.

Patient No.	Mutation	Onset	Initial presentation	Hirschsprung disease	Cardiac arrhythmias	Outcome
I	PARM (20/27)	Early (2 nd month)	Acute respiratory failure	Yes	Yes (pacemaker inserted)	Alive – home ventilation
II	PARM (20/27)	Early (1 st month)	Acute respiratory failure	No	No	Alive – home ventilation
III	PARM (20/25)	Late (4 th year)	Pulmonary hypertension	No	No	Alive – home ventilation
IV	PARM (20/27)	Early (1 st month)	Acute respiratory failure	Yes	No	Alive – home ventilation
V	PARM (20/27)	Early (1 st month)	Acute respiratory failure	Yes	Yes (fatal arrhythmias)	Dead

Table 2. Modalities of ventilatory dependence and treatment in patients with CCHS.

	<i>Hypoventilation pattern</i>	<i>Initial intubation</i>	<i>Successful extubation</i>	<i>Definitive route of ventilation</i>	<i>Mode of ventilation</i>	<i>Complications of ventilation</i>	<i>Adherence to ventilation</i>
I	Nocturnal	Infancy	No	T-tube NIV - after decannulation	PCV AVAPS	Midfacial hypoplasia (mild)	Good
II	Nocturnal	Infancy	Yes	NIV	AVAPS	Midfacial hypoplasia (mild)	Good
III	Nocturnal	-	-	NIV	PSV	Midfacial hypoplasia (mild)	Initially poor
IV	Diurnal	Infancy	No	T-tube	PC-SIMV	No	Good
V	Diurnal	Infancy	No	T-tube	PC-SIMV	No	Good

PCV - pressure control ventilation; AVAPS - average volume-assured pressure support; PSV - pressure support ventilation; SIMV - synchronous intermittent mandatory ventilation;

Ventilatory settings were adjusted to achieve and maintain PaCO₂ between 35–45 mmHg and SpO₂ >94%. The initial ventilatory parameters included either Bilevel positive airway pressure or average volume assured pressure support (AVAPS) (Table 2). Backup rates were slightly below physiologic values for the given age. Settings would be adjusted periodically through regular clinical assessments. Ventilator internal memory card manual analyses showed maintenance of sleep-disordered breathing in each patient in the first six years of life: constantly high AHI values (>5/h) were consistent with low percentage of patient-triggered breaths overnight, i.e. no more than 20% of total breaths were triggered by patients themselves during night.

Except for initial problems with adherence to NIV in a child with the late-onset disease which was resolved with time by proper accommodation, ventilation was implemented regularly. All patients on NIV had some degree of midfacial hypoplasia despite using various mask types – nasal, full-face, and custom-made when available. Facial skeleton abnormalities were not severe and had no impact on dental development.

While non-pulmonary complications were encountered in three out of four cases with 20/27 genotype, cardiac involvement was directly related to survival (Table 1). Unfortunately, ventricular arrhythmias were fatal for one child by the age of five months, even before the scheduled pacemaker insertion.

DISCUSSION

This study synthesizes a single tertiary pediatric center experience with children diagnosed with CCHS and represents ventilatory possibilities as a mandatory part of its treatment. It particularly underlines the feasibility of noninvasive ventilation at different stages of the disease.

Home mechanical ventilation has changed the long-term perspective of infants diagnosed with CCHS (13). Consequently, non-pulmonary complications nowadays have become an increasing cause of CCHS-associated mortality. Over time, technical improvements in ventila-

tory equipment and better overall health care have skewed a focus of respiratory support towards the improvement of quality of life and minimizing side effects of mechanical ventilation (13). Despite being the first option in early-onset disease with unequivocal efficacy, IMV imposed serious concerns about speech and psychosocial development (21). Additional possible complications associated with tracheostomy tube (infections, bleeding, frequent admissions for tracheostomy tube replacement) coupled with a better understanding of the nature of the disease led to the necessity of introducing NIV and broadening indications for it (15,20).

While NIV was the first-line option in CCHS for late-onset disease with nocturnal hypoventilation, there were many concerns regarding the use of NIV either after decannulation or in early-onset disease as initial treatment (20). However, awareness that there was partial maturation of chemoreceptors with time as well as diminished blunted response to both hypercarbia and hypoxia while awake has strengthened the possibility of NIV usage (22). Despite undisputed advancements in ventilatory protocols regarding CCHS, NIV can be demanding. A triangle of patients, caregivers/families, and proper equipment as main determinants is essential for a successful NIV trial. The absence of at least one of these determinants may lead to NIV failure (18). Patient-related factors are of special importance – adequate neurocognitive development and normal bulbar function firmly support the use of NIV (23). Additionally, preserved airway patency documented by bronchoscopy remains inevitable for the NIV course (24). The age of the child remains an important factor of ventilatory modality, particularly when it comes to decannulation. Namely, after the failure of an early transition from invasive ventilation to NIV had been reported, some authors suggested the period from six years to adolescence as the prime time for decannulation and introduction of NIV (15,20,25,26). Still, meticulous patient recruitment can render NIV possible after removing the tracheostomy tube, even at an early age(27).

Brain tissue in children has a relatively higher metabolic rate and basal blood flow compared to adults, with

particular vulnerability to hypoxemic episodes (28,29). Besides, decreased cerebral tissue oxygenation caused by respiratory events precedes systemic desaturation (30). Although a specific contribution of cerebral oxygenation drops in the non-rapid eye movement stage (NREM) has not been studied yet, its potential negative impact on neurocognitive outcomes should not be neglected. Thus, decannulation represents a critical part of treatment and should be meticulously considered and carried out following the international protocols (20).

Despite NIV efficacy in practically all forms of disease severity, many infants have still been ventilated invasively via tracheostomy tube for multiple reasons apart from disease severity. Challenges imposed by the appropriate mask choice, adherence to ventilation, motivation of caregivers/families and long-term sequellas of NIV such as mid-facial hypoplasia, used to play a significant role in tailoring the therapy concept (31–33). Meanwhile, improvements in ventilatory equipment associated with better overall health care of patients to CCHS have helped to cope with these challenges: different mask types adjusted to perfectly fit a child's face in combination with ventilatory software advancement have enabled early commencement of NIV (34). Moreover, mid-facial hypoplasia due to impaired growth of facial bones as a consequence of mask pressure mainly seeks observation instead of intervention (35,36). Additionally, the statement that *PHOX2B* is expressed in the rhombencephalic area important for facial development, suggested that mid-facial hypoplasia could be an integral CCHS feature instead of a mask pressure complication. Examples of invasively ventilated children with characteristic facial expressions of mid-facial hypoplasia support this remark (37). Surely, regular orthodontic follow-ups are recommended in each case (35,38). Moreover, combining different interface solutions (nasal, full-face, and custom-made masks) with family motivation is important concerning specificities of the early-childhood circadian rhythm – since the number of sleeping hours is the highest at this stage of life, problems with adherence to NIV are most frequent here.

Finally, a gradual shift from invasive ventilation to NIV – particularly with the extension of NIV to severe genotype/phenotype cases – has been conducted recently worldwide (39). Nevertheless, the necessity of long-term overnight ventilation may seemingly remain life-long, just as analyses of the percentage of patient-triggered breaths during sleep while using NIV confirmed in this study on a small-scale sample.

With improved respiratory care of the patients with CCHS, non-pulmonary complications appear to become an important factor in quality of life and overall survival. However, heterogeneous representation of cardiac arrhythmias and Hirschsprung disease was observed in patients with the same genotype in this paper. This phenotypic variability may be the result of the impact of

modifier genes, or the result of incomplete penetrability of the gene due to which the observed clinical presentation in a patient may be mild or severe (40).

This study has some limitations. The small number of patients included in the study interferes with adequate statistical analysis. Technical limitations emanated from inability to conduct full polysomnography, so a potential analysis of sleep stages associated with respiratory events was not feasible. Since *PHOX2B* genetic alterations are inherited in an autosomal dominant pattern with incomplete penetrance, it is important to analyze parents of the affected child for the *PHOX2B* pathogenic variations, since early identification of parents harboring *PHOX2B* alterations can facilitate prompt evaluation and interventions to improve long-term outcomes and enable prenatal testing (40). Lack of data related to genetic testing of some parents represents one of the limitations of this study.

CONCLUSION

Congenital central hypoventilation syndrome remains a complex condition with long-term ventilatory support as an essential therapeutic tool. Apart from invasive ventilation via tracheostomy tube as an option of choice in most children with early-onset disease, noninvasive ventilation appears to be feasible in various clinical scenarios: except for overnight ventilation in the late-onset course and after decannulation, the indication area has been widened to meticulously selected cases with the early-onset disease.

AUTHOR CONTRIBUTIONS

Each author contributed to the conception and design of the work; MB and AS contributed to the acquisition and analysis of data; MB prepared the draft of the manuscript; each author was in charge of the interpretation of data; the final version of the paper was reviewed and approved by all the authors.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ETHICAL APPROVAL

The study protocol was approved by the local Ethical committee (decision number 5/48). The research was conducted according to the Declaration of Helsinki.

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SINDROM KONGENITALNE CENTRALNE HIPOVENTILACIJE - HETEROGENOST KLINIČKE PREZENTACIJE, MODALITETI VENTILATORNE POTPORE I ISHODI

Mihail Basa¹, Jelena Višekruna¹, Bojana Gojsina Parezanović¹, Tijana Grba¹, Marina Andjelković³, Aleksandar Sovtić^{1,2}

Sažetak

Uvod/cilj: Sindrom centralne kongenitalne hipovekilacije (CCHS) predstavlja redak genetski uslovljen poremećaj karakterisan autonomnom disregulacijom i respiratornom insuficijencijom zbog koje je neophodno sprovođenje dugotrajne mehaničke ventilacije kao osnove preživljavanja. Cilj rada je predstavljanje modaliteta ventilatorne potpore u lečenju CCHS-a.

Materijal i metode: Retrospektivnom analizom medicinske dokumentacije obuhvaćeno je pet pacijenata sa dijagnozom CCHS-a lečenih u tercijarnoj pedijatrijskoj ustanovi. Alveolarna hipovekilacija dokumentovana je kontinuiranom neinvazivnom transkutanom kapnometrijom, a centralni poremećaj disanja u spavanju potvrđen je poligrafski. Dijagnostička obrada obuhvatala je i kardiološku evaluaciju, rektalnu biopsiju i analizu kateholamina u urinu. Teški poremećaji srčanog ritma predstavljali su indikaciju za implantaciju pejsmejкера. Dijagnoza bolesti potvrđena je genetskom analizom broja alaninskih rezidua u *PHOX2B* genu.

Ključne reči: centralna kongenitalna hipovekilacija, invazivna ventilacija, neinvazivna ventilacija, dekanulacija

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Rezultati: Heterogenost mutacija *PHOX2B* gena rezultovala je razlikama u kliničkom ispoljavanju bolesti. Mehanička ventilacija preko traheostome primenjivana je kod 3/4 (75%) dece sa ranim početkom bolesti u neonatalnom dobu, dok je kod jednog deteta iz date grupe uspešno sprovedena neinvazivna ventilacija (NIV). Takođe, NIV je bila opcija izbora u periodu posle dekanilmana kod jednog deteta sa ranim početkom bolesti. Konačno, NIV je sprovedena u slučaju deteta sa kasnim početkom bolesti prezentovanom simptomima plućne hipertenzije u uzrastu od četiri godine. Ventilacija je kod sve dece sprovedena redovno, a uzrok smrti u jednom slučaju bio je poremećaj srčanog rada.

Zaključak: Iako invazivna mehanička ventilacija ostaje prva terapijska opcija kod dece sa ranim oblikom CCHS-a, vremenom je došlo do proširenja indikacija za primenu NIV-a od kasnog ka odabranim slučajevima sa ranim početkom bolesti. Značaj dekanilmana i prelazak na NIV postaje sve veći u svetskim centrima.