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Congenital Central Hypoventilation Syndrome Due to a PHOX2B 20/31 Polyalanine Repeat Expansion Mutation: A Case Report

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Abstract

Congenital central hypoventilation syndrome (CCHS) is a rare autosomal dominant disorder caused by pathogenic variants in the PHOX2B gene, leading to impaired autonomic control of breathing and a blunted ventilatory response to hypercapnia and hypoxemia. We report a male infant, born at 38+5 weeks' gestation by elective cesarean section for breech presentation, who developed shallow breathing and oxygen desaturation at birth, followed by recurrent sleep-predominant apnea and progressive hypercapnia despite escalating non-invasive respiratory support. Following transfer to a tertiary neonatal intensive care unit at 11 days of age, a comprehensive evaluation excluded primary pulmonary, cardiac, neuromuscular, infectious, and metabolic causes. He was intubated on day of life 14 for worsening hypoventilation, and whole-exome sequencing confirmed a heterozygous PHOX2B polyalanine repeat expansion mutation, c.735_767dup; p.(Ala250_Ala260dup), corresponding to a 20/31 genotype. Tracheostomy was performed at approximately seven weeks of age to enable long-term mechanical ventilation. The infant's course was further complicated by respiratory colonization and infection with AmpC-producing Enterobacter cloacae, requiring carbapenem therapy. Genetic counseling confirmed that the variant had arisen de novo, with a low but non-zero recurrence risk in future pregnancies due to the possibility of parental germline mosaicism. At the time of this report, the infant remains hospitalized, clinically stable on tracheostomy mechanical ventilation, with a multidisciplinary long-term and home-ventilation plan in progress. This case highlights the importance of maintaining a high index of suspicion for congenital central hypoventilation syndrome in neonates with unexplained, sleep-predominant hypoventilation once structural, infectious, neuromuscular, and metabolic causes have been excluded, and underscores the value of genotype-informed surveillance planning and structured genetic counseling for affected families.

Categories: Genetics, Pediatrics, Pulmonology
Keywords: autonomic dysfunction, congenital central hypoventilation syndrome, enterobacter cloacae infection, genetic counseling, neonatal hypoventilation, phox2b gene mutation, polyalanine repeat expansion, tracheostomy

Introduction

Congenital central hypoventilation syndrome (CCHS) is a rare disorder of autonomic and respiratory control, first described by Mellins et al. in 1970 as a failure of automatic ventilatory regulation ("Ondine's curse") [1]. CCHS is now recognized as a neurocristopathy, a developmental disorder of neural crest-derived tissue, rather than a primary pulmonary or airway disease [2]. In 2003, PHOX2B - a transcription factor essential for autonomic nervous system development - was identified as the disease-defining gene [3]. CCHS is inherited in an autosomal dominant pattern, although the great majority of cases arise de novo, and is characterized by an inadequate or absent ventilatory response to hypercapnia and hypoxemia, most pronounced during sleep.

In simple terms, CCHS is a condition in which the brain does not reliably drive breathing, especially during sleep. Affected infants may look well while awake but breathe too shallowly or too slowly (hypoventilation), or stop breathing (apnea), when they fall asleep, so that carbon dioxide builds up and oxygen levels fall. There is no cure, and most patients need breathing support, often for life [2,4]. Because PHOX2B also guides the development of the nerves that control other involuntary body functions, some patients also have bowel problems (Hirschsprung disease), abnormal heart rhythm, or, less often, tumors arising from nerve tissue [2,4].

The estimated incidence of CCHS is approximately 1 in 200,000 live births, although this is widely regarded as an underestimate given diagnostic delays and milder, later-onset phenotypes that may go unrecognized [4]. CCHS is caused by changes in the PHOX2B gene. In about 90% of patients the change is a polyalanine repeat expansion mutation (PARM), in which the normal stretch of 20 alanine amino acids is lengthened. The genotype is written as 20/24 to 20/33, meaning 20 repeats on the normal copy of the gene and 24 to 33 repeats on the affected copy. The remaining 10% or so carry non-polyalanine repeat mutations (NPARMs), such as missense or frameshift variants, which are generally associated with more severe phenotypes [4,5]. A

growing body of literature supports a genotype-phenotype correlation, in which longer polyalanine expansions and NPARM genotypes are associated with a greater burden of continuous ventilatory dependence, Hirschsprung disease, cardiac dysrhythmia, and neural crest tumor risk [5-7]. For example, about 20% of patients with CCHS have Hirschsprung disease [6]. Cohort data illustrate this spectrum. In a 20-year single-center cohort of 24 Korean patients, 91.7% had a PARM and 8.3% an NPARM; the most common genotypes were 20/27 (45.8%) and 20/26 (33.3%); 37.5% had Hirschsprung disease; and 87.5% required a tracheostomy, with the severity of the phenotype correlating with the number of repeats [8].

We report a neonate with severe, early-onset hypoventilation ultimately attributed to a PHOX2B PARM producing a 20/31 genotype - within the higher-risk range for associated autonomic morbidity - who required intubation, tracheostomy, and continuous mechanical ventilation within the first two months of life. We describe the diagnostic pathway, clinical course to date, and genetic counseling provided, and discuss the case in the context of current CCHS literature. As the patient remains hospitalized at the time of writing, this report focuses on presentation, diagnosis, and ongoing inpatient management rather than discharge outcome.

Case Presentation

Maternal and antenatal history

The infant was born to a mother of gravida 5, para 4 obstetric history, whose pregnancy was complicated by gestational diabetes mellitus managed with dietary control and antenatal enoxaparin prophylaxis. Maternal group B Streptococcus (GBS) screening (urine culture and high vaginal swab at 35-37 weeks) was negative. Maternal HIV and hepatitis B surface antigen (enzyme-linked immunosorbent assay (ELISA)) screens were negative, venereal disease research laboratory (VDRL) was non-reactive, and rubella IgG (ELISA) was positive, indicating past immunity. Delivery was by elective lower-segment cesarean section at 38 weeks and five days of gestation for breech presentation.

Birth and early neonatal course

The infant cried immediately at birth but was noted to have shallow breathing with early oxygen desaturation; Apgar scores were 7, 8, and 9 at one, five, and 10 minutes, respectively. Oxygen saturation was 70% at 2 minutes of life with dusky coloration, prompting resuscitation with continuous positive airway pressure (CPAP; positive end-expiratory pressure (PEEP) 5-6 cm H_2O via T-piece) and supplemental oxygen (fraction of inspired oxygen (FiO_2) increased from 30% to 40%), with subsequent improvement in oxygenation. Umbilical cord blood gas showed pH 7.33, pCO_2 47.1 mmHg, pO_2 30 mmHg, and bicarbonate 25.2 mmol/L. The infant was transferred to a neonatal intensive care unit on CPAP support.

At the referring hospital, the infant was managed initially on high-flow nasal cannula (5 L/min, FiO_2 30%) but exhibited recurrent apneic episodes predominantly during sleep, with oxygen desaturation but no bradycardia. Repeat blood gas analysis showed hypercapnia ($PaCO_2$ up to 64 mmHg) with mild respiratory acidosis, prompting escalation first to CPAP and then to bilevel positive airway pressure (inspiratory positive airway pressure (IPAP) 10/expiratory positive airway pressure (EPAP) 6 cmH_2O, rate 35/min). Hypercapnia ($PaCO_2$ >55 mmHg) persisted, with only partial improvement following increases in set ventilator rate. Despite these gas-exchange abnormalities, the infant remained clinically active and hemodynamically stable, did not meet criteria for intubation at that stage, and maintained oxygen saturations >97% outside apneic episodes (falling to approximately 80% during apnea). Chest radiography and lung examination were normal throughout, and apnea was consistently most pronounced during quiet sleep - a pattern atypical for primary pulmonary or airway pathology and suggestive of a central disorder of respiratory drive.

A comprehensive evaluation was undertaken to exclude alternative etiologies. Electrocardiography was normal, and echocardiography demonstrated a patent foramen ovale with left-to-right shunt only. Neurological examination and electroencephalography were normal. Cranial ultrasound showed bilateral caudothalamic groove cystic changes, and brain magnetic resonance imaging demonstrated bilateral thin-walled subependymal (germinal matrix-related) pseudocysts with a persistent cavum septum vergae - recognized incidental neonatal findings without a known specific association with CCHS. Metabolic evaluation, including expanded newborn screening, lactate, ammonia, electrolytes, calcium, magnesium, phosphate, and creatine kinase, was within normal limits. Empiric ampicillin and gentamicin were started at birth for presumed sepsis risk but discontinued after 48 hours following a negative sepsis evaluation. Caffeine citrate was initiated and continued as maintenance therapy. The infant progressed from intravenous dextrose to full enteral feeds via orogastric tube, which were well tolerated. By day of life six, the infant remained on non-invasive (bilevel) support with persistent sleep-related hypoventilation and apnea, but was hemodynamically stable without bradycardia.

Tertiary NICU course and diagnostic confirmation

The infant was transferred to our tertiary neonatal intensive care unit at 11 days of age for suspected central hypoventilation syndrome. Non-invasive respiratory support was continued initially; however, because of progressive hypoventilation with carbon dioxide retention and persistent shallow breathing, the infant required intubation on day of life 14 and was commenced on conventional mechanical ventilation, on which

he has remained since, with stable blood gases and acceptable oxygen saturations. Early endotracheal aspirate cultures grew Enterobacter cloacae complex, prompting antibiotic escalation; subsequent endotracheal aspirate cultures were negative. Caffeine citrate was continued.

The pulmonology team reviewed the infant serially during the early weeks of admission. Genetic testing, performed through enrollment in a research whole-exome sequencing program, confirmed a heterozygous PHOX2B pathogenic variant, c.735_767dup; p.(Ala250_Ala260dup), an in-frame duplication predicting an expansion of 11 additional alanine residues and corresponding to a 20/31 PARM genotype. This finding, together with the clinical picture of apnea, hypoventilation, hypercapnia, and absent compensatory respiratory drive, was diagnostic of CCHS.

Given the genotype and clinical severity, the multidisciplinary team determined that the infant requires continuous (24 hours/day, seven days/week) ventilatory support, likely for a prolonged or lifelong duration, since even brief interruptions carry a high risk of respiratory decompensation due to inadequate spontaneous ventilation. Because CCHS patients lack an appropriate compensatory response to hypoxemia or hypercapnia, clinical deterioration may occur without overt signs of respiratory distress, underscoring the need for uninterrupted ventilatory support and continuous monitoring rather than reliance on clinical warning signs.

Airway management and tracheostomy

At approximately seven weeks of age, the infant underwent tracheostomy insertion (neonatal size 3.5 cuffless Bivona FlexTend tube (ICU Medical, San Clemente, CA, USA)) and has since been maintained on conventional mechanical ventilation via tracheostomy. The first tube change and suture removal, performed roughly two weeks later, revealed local peristomal erythema with greenish discharge, treated with topical mupirocin. Otolaryngology recommendations for ongoing tracheostomy care included keeping spare tubes (same size and one size smaller) at the bedside at all times, daily dressing changes with earlier changes if soiled, tie adjustments maintaining one finger-breadth of space from the neck, tracheal suctioning without advancing beyond the tube length, and routine tube changes every four weeks.

A follow-up pulmonology review approximately one week before the first tube change confirmed adequate ventilation on current settings, and a long-term ventilation strategy compatible with eventual home mechanical ventilation was discussed and initiated. The pulmonology team recommended gradual adjustment of ventilator settings to achieve tidal volumes of 6-8 mL/kg, reduction of the set respiratory rate toward a physiologic range (25-28 breaths per minute), a target $PaCO_2$ of 35-40 mmHg with normal pH, and continuous ventilation without interruption. The $PaCO_2$ target and the goal of uninterrupted ventilation are in line with the consensus guidelines, which recommend a $PaCO_2$ of 35-45 mmHg (ideally 35-40 mmHg in the earlier American Thoracic Society statement), an SpO_2 of at least 95%, and lifelong ventilatory support with no attempt to wean [2,4].

Infectious course

Initial empiric ampicillin and gentamicin were discontinued after three days following a negative septic workup. Approximately five weeks into the tertiary NICU admission, C-reactive protein (CRP) rose progressively (from a baseline of approximately 2 mg/L to 13.9 mg/L and then 15 mg/L over consecutive days), prompting initiation of piperacillin-tazobactam and gentamicin. CRP subsequently peaked at 81.2 mg/L, and therapy was escalated to ceftazidime. Respiratory cultures grew AmpC-producing Enterobacter cloacae, leading to a switch to meropenem and discontinuation of piperacillin-tazobactam. Meropenem was continued for a total of 14 days, after which antibiotics were stopped as inflammatory markers normalized. Blood cultures remained negative throughout. At the time of this report, the infant is colonized with AmpC-producing Enterobacter cloacae without evidence of ongoing systemic infection - a recognized consideration in tracheostomy-dependent infants requiring long-term airway access [2]. Representative laboratory values are summarized in Table *1*.

Parameter	Value	Approx. timing	Notes
Cord blood gas	pH 7.33 / pCO_2 47.1 / pO_2 30 mmHg / HCO_3 25.2 mmol/L	Birth	Mixed respiratory-metabolic picture
Peak $PaCO_2$ (pre-intubation)	Up to 64 mmHg	DOL ~1-13	Despite escalating non-invasive support
WBC	6.5 ×10⁹/L	~DOL 38	Within normal limits
MCV	88.1 fL (low)	~DOL 38	Mild microcytosis
Platelets	433 ×10⁹/L	~DOL 38	Within normal limits
CRP trend	~2 → 13.9 → 15 → peak 81.2 mg/L	~DOL 38-59	Corresponded to AmpC E. cloacae infection
Blood cultures	Negative throughout	Serial	No bacteremia
PHOX2B genotype	20/31 (c.735_767dup; p.(Ala250_Ala260dup))	~DOL 25	PARM, de novo

TABLE 1: Representative laboratory and clinical parameters

CRP, C-reactive protein; DOL, day of life; MCV, mean corpuscular volume; $PaCO_2$, partial pressure of arterial carbon dioxide; PARM, polyalanine repeat expansion mutation; WBC, white blood cell.

Nutrition

Enteral feeding was initiated on day of life one at the referring hospital and advanced gradually according to tolerance. The infant achieved full enteral feeds via tube feeding (160 mL/kg/day, administered every three hours as three feeds of expressed breast milk and five feeds of Infatrini formula daily) without evidence of feeding intolerance; abdominal ultrasound was normal.

Multidisciplinary surveillance and genetic counseling

Baseline surveillance for CCHS-associated manifestations included a repeat cranial ultrasound (unremarkable), echocardiography (normal intracardiac anatomy, function, and size), and an ophthalmologic assessment (grossly normal, with follow-up scheduled at three months).

A post-test genetic counseling session was conducted with both parents. The identified PHOX2B variant was explained to have arisen de novo - not inherited from either parent - conferring a low recurrence risk for future pregnancies, with a small residual risk attributable to possible parental germline mosaicism. The natural history of CCHS was reviewed, including its basis as a disorder of autonomic control of breathing and the potential for associated autonomic manifestations. It was explained that there is currently no curative treatment, and that management is centered on chronic assisted ventilation (particularly during sleep, though this infant requires continuous support), prevention and surveillance of complications, and optimization of overall health and development. The family was counseled on the importance of lifelong multidisciplinary follow-up spanning pediatric pulmonology, sleep medicine, cardiology, gastroenterology, oncology, ophthalmology, neurology, and neurodevelopmental pediatrics/psychology, and on potential future interventions including cardiac pacemaker placement for significant prolonged cardiac pauses, management of Hirschsprung disease or other gastrointestinal motility disorders, surveillance for neural crest-derived tumors, and early developmental intervention services. The family demonstrated good understanding, and follow-up with the genetics team was arranged.

Current status

At the time of this report, the infant remains hospitalized in the neonatal intensive care unit. He is clinically stable and adequately ventilated via tracheostomy on conventional mechanical ventilation, with ongoing titration of settings toward parameters compatible with long-term and eventual home mechanical ventilation, and continued multidisciplinary coordination for chronic disease management. Definitive discharge planning and outcome are beyond the scope of this report, as the patient remains an inpatient. The main symptoms, findings, and interventions by day of life are summarized in Table *2*.

Timing	Symptoms and findings	Data	Management
Birth (DOL 0)	Shallow breathing, early desaturation, dusky color	Apgar 7/8/9; SpO_2 70% at 2 min; cord gas pH 7.33, pCO_2 47.1 mmHg, pO_2 30 mmHg, HCO_3 25.2 mmol/L	CPAP (PEEP 5-6 cmH_2O), FiO_2 30-40%
DOL 0-10 (referring hospital)	Recurrent apnea during sleep, no bradycardia; clinically active and stable	SpO_2 >97% outside apnea and about 80% during apnea; $PaCO_2$ up to 64 mmHg with mild respiratory acidosis, persistently >55 mmHg; chest X-ray and lung examination normal	High-flow nasal cannula 5 L/min (FiO_2 30%), then CPAP, then BiPAP (10/6 cmH_2O, rate 35); still on BiPAP at DOL 6
DOL 0-10 (workup)	No alternative cause found	ECG normal; echocardiogram: PFO with left-to-right shunt; EEG and neurological examination normal; cranial ultrasound: bilateral caudothalamic groove cysts; MRI: subependymal pseudocysts and persistent cavum septum vergae; metabolic screen normal; sepsis evaluation negative	Ampicillin and gentamicin stopped at 48 h; caffeine citrate started
DOL 11	Transfer to tertiary NICU for suspected CCHS	-	Non-invasive support continued
DOL 14	Progressive hypoventilation, CO_2 retention, persistent shallow breathing	Stable gases and saturations on the ventilator afterwards	Intubation and conventional mechanical ventilation
~DOL 25	Diagnosis confirmed	PHOX2B c.735_767dup; p.(Ala250_Ala260dup), 20/31 genotype, de novo	Continuous ventilatory support planned
~DOL 38-59	Rising inflammatory markers, AmpC-producing E. cloacae	CRP about 2 → 13.9 → 15 → peak 81.2 mg/L; blood cultures negative	Piperacillin-tazobactam and gentamicin, then ceftazidime, then meropenem for 14 days
~DOL 47	Need for long-term ventilation	-	Tracheostomy (neonatal size 3.5 uncuffed Bivona FlexTend)
~DOL 60	Peristomal erythema and greenish discharge at first tube change	-	Topical mupirocin
Current (still admitted)	Clinically stable, adequately ventilated via tracheostomy	Targets: $PaCO_2$ 35-40 mmHg, tidal volume 6-8 mL/kg, rate 25-28 breaths/min	Continuous mechanical ventilation; home-ventilation plan in progress

TABLE 2: Timeline of symptoms, findings, data, and management

BiPAP, bilevel positive airway pressure; CCHS, congenital central hypoventilation syndrome; CPAP, continuous positive airway pressure; CRP, C-reactive protein; DOL, day of life; ECG, electrocardiogram; EEG, electroencephalogram; FiO_2, fraction of inspired oxygen; HCO_3, bicarbonate; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit; $PaCO_2$, partial pressure of arterial carbon dioxide; pCO_2, partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; PFO, patent foramen ovale; pO_2, partial pressure of oxygen; SpO_2, peripheral oxygen saturation. Bivona FlexTend: ICU Medical, Inc. (San Clemente, CA, USA)

Discussion

This case demonstrates the classic diagnostic pathway and severe neonatal phenotype of PHOX2B-confirmed CCHS: unexplained apnea and hypoventilation that were most pronounced in sleep, a normal cardiopulmonary and neurological workup, escalating respiratory support failure, and eventual confirmation

by genetic testing. The sleep-predominant pattern deserves particular emphasis, because it is the clinical feature that best separates CCHS from primary lung disease. In CCHS, hypoventilation is typically worse in sleep than in wakefulness, and worse in non-REM (quiet) sleep than in REM sleep, reflecting the loss of the automatic control of breathing on which breathing during sleep depends [1,2]. Affected infants have an absent or markedly reduced ventilatory response to rising carbon dioxide and falling oxygen, so the usual compensation of faster, deeper breathing does not occur, and they typically show no obvious signs of respiratory distress [2]. Our patient fits this picture. He had recurrent apneic episodes during sleep with desaturation, was otherwise active with saturations above 97% outside these episodes, and had normal chest imaging and lung examination, yet he developed progressive hypercapnia ($PaCO_2$ up to 64 mmHg) that responded only partly to CPAP and bilevel support. This mismatch between an apparently well infant with healthy lungs and significant hypercapnia is the pattern that should prompt PHOX2B testing [2,4]. It also shows why carbon dioxide must be measured and not oxygen saturation alone, since supplemental oxygen can improve saturations while worsening hypoventilation [2]. Although the early picture in this infant was sleep-predominant, longer expansions such as the 20/31 genotype are associated with continuous ventilatory dependence [5,7,9], and he subsequently required continuous mechanical ventilation. Several features merit discussion in relation to the existing literature.

Genotype-phenotype correlation

The infant's genotype - a PARM producing 31 total alanine repeats (20/31) via an 11-residue in-frame duplication - falls within the higher-risk range of PARM genotypes. Multiple cohort and case-based studies report that genotypes in the 20/27-20/33 range, alongside NPARMs, carry a disproportionately higher burden of continuous (rather than sleep-only) ventilatory dependence, Hirschsprung disease, cardiac dysrhythmia/asystole, and endocrine involvement, compared with the more common and generally milder 20/25-20/26 genotypes [5,7,9]. A Korean single-center cohort spanning 20 years similarly found a significant positive correlation between PARM repeat number and phenotype severity ($r = 0.71$, $p < 0.001$), and noted that the initial approach to ventilatory support influenced neurodevelopmental outcomes [8]. Consistent with this genotype-based risk stratification, our patient required not only sleep-related but continuous ventilatory support from early infancy, ultimately necessitating intubation and tracheostomy within the first seven weeks of life. Key published figures on CCHS are summarized in Table 3.

Feature	Reported figure	Source
Incidence	About 1 in 200,000 live births, likely underestimated	[4]
Gene change	Polyalanine repeat expansion (PARM) in about 90%; non-polyalanine repeat mutation (NPARM) in about 10%	[6]
Inheritance	Mostly de novo; asymptomatic mosaicism found in one parent in 5-10% of cases	[6]
Hirschsprung disease	About 13-20% of patients	[2,6]
Neural crest tumors	About 3-5% of patients	[2]
Milder genotypes	20/24 and 20/25: mild phenotype, often later onset	[6]
Higher-risk genotypes	20/27 to 20/33 and NPARM: autonomic features more common	[6]
Korean cohort (n = 24)	PARM 91.7%, NPARM 8.3%; genotype 20/27 in 45.8% and 20/26 in 33.3%; Hirschsprung disease 37.5%; tracheostomy 87.5%	[8]

TABLE 3: Key published figures on congenital central hypoventilation syndrome

A related body of work has specifically linked longer PARM genotypes to cardiac autonomic instability: Gronli et al. demonstrated that the proportion of children with prolonged sinus pauses (≥three seconds) on Holter monitoring, and the proportion ultimately requiring a cardiac pacemaker, rose steeply from the 20/25 to the 20/26 to the 20/27 genotype [9]. Although our patient's genotype (20/31) is longer still than those examined in that cohort, the same principle - that repeat length is a marker of cardiac autonomic risk, not merely ventilatory risk - supported the multidisciplinary plan for structured cardiology surveillance (Holter monitoring) going forward, in line with consensus recommendations [2,4].

Diagnostic approach and exclusion of alternative causes

As in most published CCHS case series, the diagnosis in this infant was one of exclusion prior to genetic

confirmation: normal chest imaging and lung examination, a structurally near-normal heart (isolated patent foramen ovale), a normal neurological examination and EEG, and a normal metabolic and newborn screening panel. This pattern - hypoventilation disproportionate to any structural or metabolic explanation, worsening specifically in quiet sleep - is the classic clinical trigger for PHOX2B testing described in the American Thoracic Society clinical policy statement and subsequent international consensus guidelines [2,4]. The incidental cranial imaging findings (subependymal pseudocysts and a persistent cavum septum vergae) are common benign neonatal findings without an established mechanistic link to CCHS and were appropriately treated as incidental rather than causal.

This case also illustrates a diagnostic pathway increasingly reported in the literature: identification of the PHOX2B variant through broader genomic testing (here, a whole-exome sequencing research program) rather than a CCHS-specific targeted assay. As next-generation sequencing panels and exome/genome sequencing become more widely used in neonatal intensive care for undifferentiated presentations, this route to diagnosis may become more common, though targeted PHOX2B repeat-length analysis remains the more sensitive first-line test specifically for PARM sizing and should be pursued directly whenever CCHS is the leading clinical suspicion [2].

Ventilatory management

Our patient's management trajectory - initial non-invasive support, escalation to intubation and conventional mechanical ventilation, and subsequent tracheostomy - mirrors the most common pathway described in the literature for patients requiring continuous ventilatory support in infancy. In a 20-year single-center Korean cohort, tracheostomy was ultimately used in 87.5% of patients despite growing interest in earlier transition to non-invasive ventilation, reflecting both the severity of continuous-dependence genotypes and the practical safety margin tracheostomy affords in very young infants [8,10]. The 2010 American Thoracic Society statement recommended tracheostomy with positive-pressure ventilation in the first years of life [4]. The 2020 European guidelines describe it as the most commonly used method in that age group, recommended on the assumption that it gives better gas exchange and neurocognitive development, but they note that no evidence compares its outcomes with those of early mask ventilation, which may be considered in selected infants with close monitoring [2]. Transition to mask ventilation or phrenic nerve pacing can be considered later in childhood in selected patients [2]. The $PaCO_2$ target adopted for this infant (35-40 mmHg) lies within the range recommended by the guidelines (35-45 mmHg), as does the goal of continuous, lifelong ventilation [2,4]. The specific tidal volume (6-8 mL/kg) and respiratory rate (25-28 breaths per minute) targets reflect the recommendations of the treating pulmonology team and are not specified in the guidelines.

Tracheostomy in infants: recommendations and risks

Guidelines give specific advice for infants who receive a tracheostomy. The CCHS guidelines recommend performing it as soon as technically possible after diagnosis in newborns and young infants, using uncuffed cannulas to reduce the risk of tracheomalacia and, provided ventilation stays adequate, the smallest suitable size, with the cannula size adjusted as the child grows [2]. They also recommend pressure-controlled ventilation, warming and humidification of inspired gas, and airway assessment by fiber-optic tracheoscopy or bronchoscopy when new symptoms appear, after a change of cannula size or type, before decannulation, and every three to six months during the first two years after tracheostomy [2]. Our patient's uncuffed neonatal tube and the care plan recommended by otolaryngology are in keeping with these recommendations.

The risks of infant tracheostomy are well documented and are the main reason for the intensive caregiver training that precedes discharge. In CCHS, the recognized complications include infection, accidental decannulation, cannula obstruction, granulomas, tracheomalacia, and tracheocutaneous fistula after decannulation, as well as interference with feeding and delayed speech development [2]. A systematic review of pediatric tracheostomy found complications in 0-90% of series, with a mean of about 40%; accidental decannulation and cannula obstruction each accounted for about 8% of reported complications, and procedure-related mortality reached up to 6%, mainly from obstruction or accidental decannulation [11]. Younger age, low birth weight, and prematurity were associated with more complications, partly because of the small airway and cannula [11]. Our patient's peristomal erythema with discharge after the first tube change and his airway colonization with AmpC-producing Enterobacter cloacae illustrate the infective risks. These are relevant to antibiotic choice over his anticipated lifelong tracheostomy dependence and underline the importance of vigilant stomal and airway care.

Because obstruction or accidental decannulation can be fatal within minutes, guidelines place great emphasis on preparing for discharge. The pediatric chronic home ventilation guideline recommends an awake, attentive, and trained caregiver in the home at all times, at least two trained family caregivers, standardized discharge criteria, and a medical home co-managed by a generalist and a respiratory specialist [12]. The CCHS guidelines add a back-up ventilator, overnight pulse oximetry with alarms, and periodic PCO_2 monitoring [2]. These requirements are relevant to the home-ventilation plan now in progress for our patient.

Genetic counseling and recurrence risk

Consistent with the majority of CCHS cases, this variant occurred de novo. Most parents of affected children do not carry the PHOX2B variant found in their child, which suggests that the variant arose after fertilization or in one of the parental gametes [2]. Even so, a negative parental result does not remove the risk of recurrence. Some apparently unaffected parents carry a low-penetrance variant in all of their cells, and others are somatic mosaics who carry a fully penetrant variant in only some of their cells. A parent who carries the variant in all cells has a 50% risk of transmitting it to each child, whereas the risk with proven somatic mosaicism is lower but cannot be quantified [2]. Parents who test negative for both constitutive and mosaic variants may still carry the variant in a proportion of their germ cells (germline mosaicism). Standard testing cannot detect this, and it can only be demonstrated when a second affected child is born to an asymptomatic couple who do not carry the variant [2]. For this reason, the guidelines advise offering parental testing once a variant is found in the child, and prenatal genetic testing in every family with an affected child, whether or not a parent is a carrier [2]. Prenatal diagnosis can also help early postnatal planning, since an affected infant should be born in a centre able to start ventilation at once [2]. Inheritance is autosomal dominant, so our patient will himself have a 50% risk of transmitting the variant to his own children, and the guidelines advise that pregnancy in patients with CCHS be planned only after genetic counseling [2]. The distinction between a low but non-zero recurrence risk and no risk is an important point of family counseling, and it was conveyed to this family.

Strengths and limitations

This case adds to the relatively limited number of detailed, genotype-confirmed reports describing the acute neonatal presentation and early inpatient course of a higher-risk PARM genotype (20/31), an expansion length less commonly reported than the more frequently described 20/25-20/27 genotypes. It also documents diagnosis via research-based exome sequencing rather than targeted testing, and highlights a clinically relevant infectious complication in the early tracheostomy period. A limitation of this report is that, because the infant remains hospitalized, longer-term respiratory, neurodevelopmental, and autonomic outcomes cannot yet be described; a follow-up report will be valuable once home ventilation is established and longitudinal outcomes are available. In addition, detailed laboratory and bioinformatic methods of the exome sequencing were not available to the authors.

Conclusions

This report describes a neonate with genetically confirmed CCHS due to a PHOX2B 20/31 PARM genotype, an expansion length that is rarely reported. CCHS is a recognized entity, and this case does not change its definition. Its value lies in what it illustrates for clinicians who may meet the condition. First, sleep-predominant hypoventilation with healthy lungs and a normal cardiac, neurological, and metabolic workup should prompt measurement of carbon dioxide and early PHOX2B testing, because oxygen saturation alone can mislead. Second, a long expansion such as 20/31 tends to give a severe course, in this infant with continuous ventilation and a tracheostomy within the first weeks of life, and it calls for surveillance planning for the associated autonomic features. Third, infant tracheostomy carries real infective and airway risks that need to be planned for before discharge. Finally, parents need clear counseling that a de novo finding still leaves a small recurrence risk through germline mosaicism, with prenatal testing available. Coordinated multidisciplinary care from the time of diagnosis remains central to management.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Ahmed Mabrouk, Ahmed Elajab, Khaled El-Atawi

Drafting of the manuscript: Ahmed Mabrouk

Supervision: Ahmed Mabrouk

Critical review of the manuscript for important intellectual content: Ahmed Elajab, Khaled El-Atawi

Disclosures

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submitted work.

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