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REVIEW ARTICLE

Adult-onset congenital central hypoventilation syndrome due to *PHOX2B* mutation

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Abstract

Central hypoventilation in adult patients is a rare life-threatening condition characterised by the loss of automatic breathing, more pronounced during sleep. In most cases, it is secondary to a brainstem lesion or to a primary pulmonary, cardiac or neuromuscular disease. More rarely, it can be a manifestation of congenital central hypoventilation syndrome (CCHS). We here describe a 25-year-old woman with severe central hypoventilation triggered by analgesics. Genetic analysis confirmed the diagnosis of adult-onset CCHS caused by a heterozygous de novo poly-alanine repeat expansion of the *PHOX2B* gene. She was treated with nocturnal non-invasive ventilation. We reviewed the literature and found 21 genetically confirmed adult-onset CCHS cases. Because of the risk of deleterious respiratory complications, adult-onset CCHS is an important differential diagnosis in patients with central hypoventilation.

Keywords Central congenital hypoventilation syndrome · *PHOX2B* · Polyalanine repeat expansion mutation · Hirschsprung disease · Neural crest tumours · Autonomic

Key points
Be aware of LO-CCHS if unexplained hypoventilation.
There might be subtle symptoms indicative of CCHS during childhood.
Consider other symptoms, signs and related disorders besides hypoventilation.
Consider complete genetic work-up if screening test is negative because of the importance of genetic diagnosis for patient, offspring and parents.
Longer PARMs or non-PARMs usually have a more severe course.
Be aware of the use of respiratory depressant medications.
CCHS patients don't outgrow the disorder and require lifelong treatment.
CCHS: congenital central hypoventilation syndrome, LO-CCHS: later-onset CCHS.

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Introduction

Congenital central hypoventilation syndrome (CCHS, OMIM 209880) is a rare neurocristopathy, with an estimated incidence of 1 in 50,000–200,000 live births [1, 2]. First described in 1970, the genetic origin was identified by mutations in the paired-like homeobox 2B gene (*PHOX2B*, OMIM 603851) [3, 4]. There are about 1000 cases with genetically confirmed CCHS reported worldwide, with a male-to-female ratio of 1:1 [1]. An association with Hirschsprung disease (HSCR) has been reported [5]. CCHS is typically characterised by a classic presentation in newborns and, rarely, a milder later-onset (LO-CCHS) presentation in toddlers, children and adults. *PHOX2B* is a transcription factor with expression outside the central nervous system restricted to neurons of chromaffin cells of the autonomic nervous system expressed by sympathetic, parasympathetic and enteric ganglia, adrenal and extra-adrenal chromaffin cells and by glomus cells [6]. *PHOX2B* has a function in respiratory control and respiratory drive at the level of the brainstem [7]. Ninety percent of patients have a heterozygous polyalanine repeat expansion mutation (PARM) within exon 3 of *PHOX2B*, located on chromosome 4p13. Expansions of 26 repeats or higher are considered full-penetrance alleles [2, 8]. Severe phenotypes in newborns with need for continuous ventilation, association with neural crest tumours, namely tumours of the sympathetic nervous system (neuroblastoma, ganglioneuroblastoma, ganglioneuroma) and HSCR, as well as other functional impairments of the autonomic nervous system is seen in patients with longer PARMs or non-PARMs [1, 9, 10]. The mildest central hypoventilation phenotype is seen in patients with repeat lengths of 24 or 25 and presents primarily after exposure to respiratory depressants or respiratory infections, though phenotypes differ across family members carrying the same mutation [1, 11].

Methods

We describe a patient with pharmacologically triggered adult-onset CCHS and reviewed the literature of adult-onset CCHS. Because LO-CCHS is the term used for cases with onset of 1 month and older, we used LO-CCHS as search term, but combined this with search term ‘adult’. 21 cases of LO-CCHS with adult-onset are reported. We refer to these cases and our novel case as adult-onset CCHS.

Case report

A 25-year-old woman without significant medical history was admitted to another hospital because of presumed intoxication with paracetamol taken for pain due to premolar root canal treatment the day before. Acetylcysteine treatment was initiated but no biochemical arguments of hepatic failure were revealed. Analgesic treatment with oral oxycodone 5 mg, oral tramadol 100 mg and intravenous piritramide 20 mg was given. Subsequently, she developed hypoventilation and loss of consciousness with need for naloxone, intubation and sedation with propofol for respiratory support. During intubation, she experienced two generalised tonic–clonic seizures for which levetiracetam was started, complicated with aspiration pneumonia. After a few hours, she was extubated with persisting hypoventilation and carbonarcosis treated with non-invasive ventilation. CT scan of the head with angiography and lumbar puncture revealed no abnormalities. After 3 days, she was referred to our centre. History taking revealed complaints of hypersomnolence without snoring since months and concentration difficulties during studying. Clinical neurological examination was normal, besides hypersomnolence at time of hypoventilation. Questioning her mother, as a child there was a period of cyanosis without clear explanation. A curettage was performed in 2017 because of missed abortion at 11 weeks.

Arterial blood gas analysis upon admission showed type 2 respiratory failure [pH 7.25 (7.35–7.45), PCO_2 81 mmHg (32–45), PO_2 78 mmHg (83–108), bicarbonate 35 mmol/l (22–26)]. Blood ammonia was slightly elevated [58 µmol/l (11–48)]. Chest X-ray, electrocardiography, brainstem evoked potentials, sympathetic skin response, heart rate variability, ultrasound of the diaphragm excursions, transthoracic echocardiography, spirometry and cerebrospinal fluid analysis were normal besides mild dextro-scoliosis. MR scan of brain (Fig. 1) revealed an impression from the left vertebral artery at the origin of the posterior inferior cerebellar artery at the left medulla oblongata without signal alteration of the medulla. CT scan of the cervical spine revealed no significant changes. Polysomnography was suggestive for (central) hypoventilation with hypoxemia and hypercapnia (results of the polysomnography are included in the supplementary appendix). Nocturnal capnometry using a Sentec

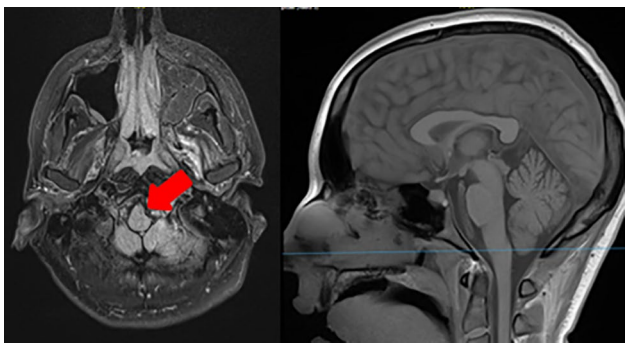

Fig. 1 Impression from the left vertebral artery at the origin of the posterior inferior cerebellar artery at the left medulla oblongata without signal alteration of the medulla (red arrow) (color figure online)

Device confirmed nocturnal desaturation until 51% and a mean nocturnal PCO_2 of 67 mmHg. Electroencephalography was moderately slowed (6.5 Hz), but normalised (9 Hz) after non-invasive ventilation as was the case for the arterial blood gases. Screening for neoplasia and paraneoplastic syndromes was negative. CCHS was considered and genetic analysis of *PHOX2B*, including PCR amplification of all three coding exons followed by fragment analysis and sequencing, was started. This revealed a de novo heterozygous PARM of 25 repeats in exon 3 (20/25 genotype) and confirmed the diagnosis of CCHS in this patient. There was a delayed and inadequate ventilatory response to increasing PCO_2 measured during wakefulness. After initiation of non-invasive ventilation, which leads to a complete night-time PCO_2 correction, she was discharged for home ventilation 21 days after admission. Seventeen months after presentation she is doing well on continued treatment.

Congenital central hypoventilation syndrome

Diagnostic criteria

Criteria of CCHS, shown in Table 1, have been postulated as '1' persistent central alveolar hypoventilation during sleep detected by polysomnography, while the patient spontaneously breathed room air, '2' no primary lung, neuromuscular, cardiac or brainstem abnormalities that could explain the hypoventilation and '3' absent or markedly reduced hypercapnic ventilatory response [12, 13]. The requirement of a confirmed *PHOX2B* mutation was added in the American Thoracic Society 2009 Policy Statement on CCHS [1, 11]. While CCHS is a rare disorder, reports on adult-onset forms are even more scarce. A review of the literature revealed 21 reported genetically confirmed adult-onset CCHS cases, summarised in Table 2 and supplementary Table S1 [8, 10, 11, 14–22].

Pathophysiology

Spontaneous breathing is an automatic process and depends on a central pattern generator located in the brainstem including neurons in the dorsolateral pons, nucleus of the solitary tract and ventrolateral medulla (ventral respiratory column). The dorsal respiratory group relays information from peripheral chemoreceptors and pulmonary mechanoreceptors. The ventral respiratory column controls the activity of inspiratory or expiratory motor neurons and contains a group of neurons critical for respiratory rhythmogenesis, the so-called pre-Bötzinger complex [23]. The retrotrapezoid nucleus (RTN), located in the rostral medulla oblongata, innervates exclusively the respiratory pattern generator neurons. The RTN receives afferent chemosensory information and its glutaminergic neurons, that are non-aminergic and express homeodomain transcription factor *PHOX2B*, respond vigorously to increases in local PCO_2 [24]. It was recently shown that anaesthetic drugs like isoflurane and opiates like morphine potentiate aggregation and mislocalization of *PHOX2B* variants similar to that seen in CCHS. These drugs may so hinder folding and activity of proteins leading to activation of endoplasmic reticulum stress pathways, eventually affecting neuronal function [7]. This effect of anaesthetics and opiates may explain their role as a trigger for LO-CCHS in patients carrying a *PHOX2B* mutation. Normally, people can voluntarily alter respiration because of higher cortical input to the brainstem. In addition, adult-onset CCHS patients breathe almost normally. Pre-inspiratory potentials generated at the supplementary motor area likely play a role in modulation in awake normal humans and are significantly more frequent in CCHS patients. These findings suggest that the supplementary motor area contributes to the wakefulness drive to breath by facilitating the response of spinal motor neurons to the residual bulbospinal drive to breath [25].

Signs, symptoms and neuroimaging

Besides an inadequate response to hypercapnia and hypoxia, particularly during sleep, CCHS consists of a broader range of symptoms and signs, as well as related diseases (see Table 3) [1, 10, 26–28]. In our case series of 22 patients with genetically confirmed LO-CCHS, no gastro-intestinal problems were reported. In a case series of 27 CCHS patients, gastro-intestinal disorders as dysphagia (4%), gastro-intestinal reflux disease (4%) and constipation (15%) were seen [29]. Neurological, cardiac, autonomic nervous system and dermatological abnormalities were all present in our case series. Neurological symptoms were most frequently described with morning headaches in 23%, excessive daytime sleepiness or fatigue in 32% and cognitive deficits or confusion in 32% of patients. Interestingly, as intellectual and cognitive deficits are described, one study found corpus callosum and precuneus thinning, contributing to visuospatial deficits and hippocampal–fornix–mamillary body injury contributing to temporal cortical thinning with resulting deficits in planning and memory. A third cortical thinning pattern in the anterior cingulate cortex develops from axonal loss of the cingulum bundle and likely contributes to loss of dyspnoea and to additional affective characteristics in the syndrome, including an impaired sense of self-care [26]. Seizures were present in 23% of LO-CCHS patients, but another case series reported a higher number of CCHS patients with seizures (21/39; 54%) [30]. The most

Table 1 Characteristics of symptomatic patients diagnosed with adult-onset central hypoventilation syndrome and confirmed *PHOX2B* mutation [8, 10, 11, 14–22]

No.	Article	Sex/age at D/ (y)	Trigger	Symptoms and signs at onset	Mutation in *PHOX2B*	Hereditary	Treatment	Blood gas/ biochemistry at admission	PSG
1	Meylemans et al. 2020 (present case)	F/25	Analgesia	Hypersomnolence (since mo), hypoventilation, coma, GTCI Normal to mild reduced basal body temperature, mild bradycardia and mild hypertension first days of admission	PARM 20/25	De novo, no children	BiPAP → nocturnal nasal mask BiPAP	pH 7.254, $PaCO_2$ 81.3 mmHg, PaO_2 78.2 mmHg, HCO_3^-35.2 mmol/l, base excess 6 mmol/l), Ammonium 58 µmol/l, Hc 32.9%	AHI 0.0/h, SpO_2 nadir (REM) 75%, SpO_2 nadir (NREM) 50.3%, TST SpO_2 <88% 37%. Most of time NIV. During short registration without NIV progressive decreasing NAF amplitude with decreasing SpO_2 and increase in PCO_2. Suggestive for central hypoventilation with hypoxemia and hypercapnia
2	Lombardo et al. 2017 [10]	F/30	No	Daytime somnolence, occasionally waking during the night with sensations of breathlessness, periods of sleep apnoea lasting longer than 10s with frequent night time arousals	Exon 1 c.234C>G ∫	Daughter and son: CCHS + HSCR, both *PHOX2B* exon 1 c.234C>G	NA	NA	NA
3	Chuen-im et al. 2014 [11]	F/42	Gallbladder surgery	Hypoventilation , complex sleep apnoea	PARM 20/24	Daughter PARM20/24. Granddaughter LO-CCHS, PARM 20/24	O_2 supplementation and nocturnal NIPPV	NA	Hypoventilation, central hypersomnia and chronic hypercapnic respiratory failure
4	Visser et al. 2013 [14]	F/55	NA	Sleep-disordered breathing	'Mild mutation'	NA	Nocturnal NIV – BiPAP (+ oral theophylline)	NA	Performed, but result NA
5	Lamon et al. 2012 [15]	F/48	Ovarian cyst surgery	Severe hypoventilation requiring intubation	PARM 20/25	NA	NA	pH 7.22, $PaCO_2$ 80 mmHg, PaO_2 50 mmHg	Numerous central and obstructive apnoeas and hypopneas, with severe hypoxaemia and hypercapnia

Table 1 (continued)

No.	Article	Sex/age at D/ (y)	Trigger	Symptoms and signs at onset	Mutation in *PHOX2B*	Hereditary	Treatment	Blood gas/ biochemistry at admission	PSG
6	Meguro et al. 2012 [16]	F/35	No	'LO-CCHS'	PARM 20/25	Son CCHS, PARM 20/25	NA	NA	Performed, but result NA
7	Meguro et al. 2012 [16]	M/33	No	'LO-CCHS'	PARM 20/25	Brother of No 6	NA	NA	Performed, but result NA
8	Meguro et al. 2012 [16]	F/68	No	'LO-CCHS'	PARM 20/25	Mother of No 6	NA	NA	Performed, but result NA
9	Bittencourt et al. 2012 [17]	M/49	NA	Severe headache, excessive daytime sleepiness , cold hands, muscle pain, memory deficits, cyanosis, sleep apnoea	PARM 20/25	Son CCHS, PARM 20/25	Nocturnal nasal mask VPAP→ after 2y nasal mask NIV night and day → after 1y tracheotomy and nocturnal IV	pH NA, $PaCO_2$ 85 mmHg, PaO_2 57 mmHg, Hc 65%, EPO 173.5 IU/ml	Non-apnoeic oxygen desaturation, TST SpO^2 <85% 70%, predominantly central apnoea (AHI 24.1/h), mean $ETCO_2$ 57mmHg
10	Parodi S et al. 2010 [18]	F/26	No	Early morning headaches, daytime drowsiness, frequent episodes of sleep paralysis in which she felt awake but unable to move and speak	PARM 20/25,	De novo, daughter CCHS, PARM 20/25	Nocturnal nasal mask NIV with PS	pH NA,$PaCO_2$ 26–30 mmHg, PaO_2 NA	Several episodes of hypopneas without signs of airway obstruction, absent response to hypercapnia. SpO_2 75% after few minutes of sleep with nadir of 50% at 30min. More prominent hypoventilation in NREM, also in REM. Mean SpO_2 78%, TST SpO_2 <85% 95%. PCO_2 ranges 67–75mmHg
11	Lee et al. 2009 [19]	M/adult	NA	Central hypoventilation	PARM 20/25	Parent of No 12 and 13.	BiPAP	Hypoxia and hypercapnia, Hc 70%	Performed, but result NA
12	Lee et al. 2009 [19]	NA/adult	NA	Impaired hypercapnic ventilatory response	PARM 20/25	2nd child of No 11	NA	Performed, but result NA.	Performed, but result NA
13	Lee et al. 2009 [19]	NA/adult	NA	Impaired hypercapnic ventilatory response	PARM 20/25	3th child of No 11	BiPAP	Performed, but result NA.	Nocturnal hypoventilation nadir SpO_2 59%

Table 1 (continued)

No.	Article	Sex/age at D/ (y)	Trigger	Symptoms and signs at onset	Mutation in *PHOX2B*	Hereditary	Treatment	Blood gas/ biochemistry at admission	PSG
14	Trochet et al., 2008 [8]	M/25	No	'LO-CCHS'	PARM 20/25	Daughter LO-CCHS, PARM 20/25	Nocturnal ventilation	NA	NA
15	Trochet et al. 2008 [8]	F/55	Anaesthesia	Respiratory arrest	PARM 20/25	Son and granddaughter CCHS, both PARM 20/25	NA	NA	NA
16	Trochet et al. 2008 [8]	M/40	NA	Sleep apnoea at age 40 years	PARM 20/28	Child CCHS + HSCR-LS, PARM 20/28	Nocturnal CPAP	NA	NA
17	Barrat et al. 2007 [20]	M/41	No (RI in past?, see table S1)	Ankle swelling, morning headaches, low mood, hypersomnolence since 2 mo. Drowsy, confused, oedema to mid-thigh	PARM 20/25	Not determined, no children	Continues nasal mask NIPPV→ after 2 days nocturnal NIPPV	pH 7.21, $PaCO_2$ 77.3 mmHg, PaO_2 64.5 mmHg, Hc 64%	NA
18	Antic NA et al. 2006 [21]	M/22	URI	Abnormally low pulse oximetry reading, 'LO-CCHS'	PARM 20/25	No children or not affected	Nasal mask BiPAP, almitrine bismesylate 50mg 2dd → nocturnal BiPAP	pH 7.42, $PaCO_2$ 63 mmHg, PaO_2 36 mmHg, HCO_3^- 37 mmol/l, Hc 55%	Nocturnal oximetry <50% without NIV due to apnoea within 30min of sleep onset.
19	Antic NA et al., 2006 [21]	M/22	No	Daytime sleepiness, cyanotic	PARM 20/25	No children or not affected	Nasal mask BiPAP→ nocturnal BiPAP	pH 7.32, $PaCO_2$ 60 mmHg, $PaO^2$56 mmHg, HCO_3^-30 mmol/l, Hc 77%	Severe hypoxemia (nadir SpO_2 71%), hypercapnia ($TcpCO_2$ 82mmHg) in NREM. No REM sleep.

Table 1 (continued)

No.	Article	Sex/age at D/ (y)	Trigger	Symptoms and signs at onset	Mutation in *PHOX2B*	Hereditary	Treatment	Blood gas/ biochemistry at admission	PSG
20	Antic NA et al. 2006 [21]	F/27	No, worse with benzodiazepine	Probable epileptic seizure, confused, poorly arousable, partus 2nd child 8d before. At ED 2 epileptic seizures, after lorazepam apnoea requiring intubation. Persistent fatigue	PARM 20/25	Son LO-CCHS, daughter CCHS, both nocturnal mechanical ventilation via tracheostomy, both PARM 20/25	Nasal mask BiPAP→ nocturnal BiPAP	NA	Central hypo/apnoea, severe hypoxemia (nadir SpO_2 40%), hypercapnia $TcpCO^2$72mmHg NREM, only 8min REM.
21	Antic NA et al. 2006 [21]	F/36	No (URI and anaesthetic in past?, see table S1)	Increasing seizure frequency, unresponsive to medication	PARM 20/25	Both children CCHS, PARM 20/25	Nasal mask BiPAP → nocturnal BiPAP	$PaCO_2$ 36 mmHg, Hc nl	Severe hypoxemia (SpO_2 nadir 52%), AHI 3.2/h, subtle hypopneas and hypoxemia out of proportion.
22	Weese-Mayer DE et al. 2005 [22]	M/35	- Spontaneous - UPPP?	- "Snoring for his whole life, nocturnal gasping, stopping breathing, turning blue" - Readmission 2 days after UPPP because of intermittent confusion, difficulty staying awake, respiratory failure, severe headache Temperature 35.5 °C	PARM 20/25	2 daughters LO-CCHS, both PARM 20/25, older daughter nocturnal mechanical ventilation via tracheostomy, younger daughter nocturnal nasal cannula oxygen	- Nasal mask BiPAP (intolerance) → after 6 mo UPPP - intubation, mechanical ventilation, tracheotomy → BiPAP	pH 7.3 (on 2l O_2/min), $PaCO_2$ 68 mmHg, PaO_2 78 mmHg, HCO_3^- 36 mmol/l), Hc 73%	Alveolar hypoventilation with hypoxemia (nadir SpO_2 76%), hypercapnia $TcpCO_2$ 60mmHg).

∫: nonsense mutation, replaces a tyrosine residue and premature stop codon, producing truncated protein. Case no. 2, 6, 7, 8, 10 and 21 were diagnosed after a confirmed diagnosis of CCHS in a family member.

Only the abstracts of references [15] and [19], respectively Lamon et al. 2012 and Lee et al. 2009, were available

AHI apnoea/hypopnea index, *BiPAP* Bilevel positive airway pressure, *CCHS* congenital central hypoventilation syndrome, *CPAP* continuous positive airway pressure, *dd* daily dose, *D/* diagnosis, *ED* emergency department, *EPO* erythropoietin, $ETCO_2$ end-tidal pressure of CO_2, *F* female, *GTCI* generalized tonic–clonic seizures, *h* hour, *Hc* haematocrit, *HSCR* Hirschsprung disease, *HSCR-LS* Hirschsprung disease long-segment, *IV* invasive ventilation, *LO-CCHS* later-onset congenital central hypoventilation syndrome, *M* male, *min* minutes, *Mo* months, *NA* not available, *NAF* nasal airway flow, *NIPPV* non-invasive positive pressure ventilation, *NIV* non-invasive ventilation, *Nl* normal, *No.* number, *NREM* non-rapid eye movement sleep, *PARM* polyalanine repeat expansion mutation, *PS* pressure support, *PSG* polysomnography, *REM* rapid eye movement sleep, *RI* respiratory infection, *s* seconds, *TcpCO2* peak transcutaneous pCO2, *TST* total sleep time, *UPPP* uvulopalatopharyngoplasty, *URI* upper respiratory tract infection, *VPAP* various positive airway pressure, *y* year

Table 2 Criteria of congenital central hypoventilation syndrome [13]

1	Generally, adequate ventilation while awake and at rest and apparent hypoventilation with monotonous respiratory rate and shallow breathing (diminished tidal volume) during sleep OR apparent hypoventilation while both awake and asleep
2	Absent perception of asphyxia (i.e., absent behavioural awareness of hypercapnia and/or hypoxemia) and absent arousal from sleep with development of physiologic compromise secondary to hypercapnia and/or hypoxemia
3	Hypoventilation with absent or attenuated ventilatory response to hypercapnia and/or hypoxemia when awake and asleep
4	No evidence of primary neuromuscular, lung, or cardiac disease or identifiable brain stem lesion that could account for the full constellation of signs and symptoms including ANSD
5	Confirmed *PHOX2B* mutation
6	Symptoms of ANSD including but not limited to severe breath-holding spells; lack of physiologic responsiveness to the challenges of exercise and environmental stressors; diminished pupillary light response; oesophageal dysmotility; severe constipation even in the absence of Hirschsprung disease; profuse sweating; reduced basal body temperature; and altered perception of anxiety

Later-onset congenital central hypoventilation syndrome if presentation after 1 month of life

ANSD autonomic nervous system dysregulation

Table 3 Symptoms and signs

Respiratory	Autonomic nervous system dysregulation
Inadequate ventilatory response to hypercapnia and hypoxia	Abnormal pupillary light reaction
Hypopneas/apnoea	Abnormal sweating pattern
Dyspnoea	Abnormal heart-rate variability
Breath-holding spells without air hunger (e.g. abnormal underwater swimming capacity)	Impaired glucose homeostasis
Snoring	Reduced body basal temperature
Limited breath-to-breath variability	Lack of physiological responsiveness to exercise and environmental factors
Cardiac	**Neurological**
Attenuated increase in heart rate in response to exercise	Daytime sleepiness
Increased frequency of bradycardia and transient asystole, with rhythm disturbances severe enough to warrant permanent cardiac pacemaker insertion	Fatigue, drowsiness
	Confusion
	Morning headaches
Decreased heart beat-to-beat variability	Altered perception of anxiety
Lower awake and higher asleep blood pressure	Seizures
Right heart failure	Intellectual and cognitive deficits (visuospatial, planning, memory deficits, affective characteristics including impaired sense of self-care)
cor pulmonale	
Gastro-intestinal	**Facial/dermatological**
Oesophageal dysmotility	Cyanosis
Dysphagia	Swelling/oedema of ankles and feet
Hirschsprung disease	Characteristic facies (box-shaped, short and flat)
Biochemical	**Other**
Hypoxia	Strabismus
hypercapnia	Hypothalamic dysfunction
Polycythaemia	Neural crest tumours (neuroblastoma, ganglioneuroblastoma, ganglioneuroma)
Elevated haematocrit	

reported cardiac abnormality was cardiac hypertrophy or failure in 27% of patients, all males. Blood pressure abnormalities, bradycardia and transient asystole were less frequently reported. Gronli JO, et al., reported that *r–r* interval prolongation ≥ 3 s was seen in 38% of CCHS patients. None of these patients had PARM 20/25 genotype and there was an increasing incidence with increasing repeat length [30]. Five patients (23%) had cyanosis and one (4%) had oedema. Although strabismus is described in the literature to be present in about 50% of CCHS patients, this was not herhalded in our case series of LO-CCHS. Also, the prevalence of pupillary abnormalities is reported to be as high as 70%,

but only 9% in the LO-CCHS described here [1]. Given the aforementioned symptoms, a list of differential diagnoses needs to be considered (see Table 4).

Associated disorders

HSCR, a congenital malformation of the hindgut which occurs as an isolated trait in 70% of cases, but which occasionally is associated with other congenital anomalies, has been estimated to be associated with CCHS in 1.5% of cases, while 20–50% of patients with CCHS have HSCR [27]. HSCR is associated in 19% of CCHS with PARM and in 80% of CCHS of non-PARM [28]. None of the 22 adult-onset CCHS cases were associated with HSCR, but in some cases, the disease was present in the offspring [8, 10].

Neural crest tumours (neuroblastoma, ganglioneuroblastoma, ganglioneuroma) are present in about 5–10% of CCHS. Neuroblastoma estimated risk incidence in CCHS with non-PARM is 41–50% and in CCHS with PARM 1% [10, 21, 28]. No neural crest tumour in the adult-onset CCHS cases or their offspring were seen [8, 10, 11, 14–22].

LO-CCHS in association with hypothalamic dysfunction is described in association with a PARM with 25 repeats as well as a missense mutation in exon 1 not affecting the homeodomain [31]. Other LO-CCHS cases are differentiated from rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome which lack *PHOX2B* mutations. ROHHAD typically presents between the ages of 1.5 and 7 years with rapid onset obesity [28]. No hypothalamic dysfunction was heralded in the listed adult patients [8, 10, 11, 14–22].

Autonomic nervous system disorders (ANSD) have also been reported as part of the neurocristopathy. ANSD were reported in four adult-onset CCHS cases, including our case, namely the non-PARM case and three PARM 20/25 cases. Pupillary abnormalities were present in two patients including the non-PARM case. One patient had transient asystole and two patients had low body temperature, all PARM 20/25 cases.

Genetics and confirmation of diagnosis

Most of the patients have a heterozygous PARM within exon 3 of the *PHOX2B* gene with repeat length ranging from 24–33, affecting the homeodomain. The normal length is 20 repeats. Expansion of five alanines is by far the most

Table 4 Differential diagnosis

Respiratory
Severe prematurity (apnoea of prematurity)
Acquired hypoventilation
Obstructive sleep apnoea (e.g. adenotonsillar hypertrophy, obesity, muscle weakness and craniofacial anomalies)
Genetic
Paediatric obesity–hypoventilation syndrome (e.g. ROHHAD, Prader–Willi syndrome, LO-CCHS/HD)
Familial dysautonomia (Riley–Day syndrome)
Neurological
Neuromuscular disorder (e.g. paediatric botulism, dystrophia myotonica, myasthenia gravis)
Brainstem lesion
Infectious or (auto-)immune encephalitis (e.g. bulbar poliomyelitis, syphilis, sarcoidosis of the central nervous system)
Trauma
Tumour
Infarction
Structural abnormality (e.g. os odontoideum, cervical syringomyelia, Chiari type II malformation)
Gastro-intestinal
Aspiration syndromes
Cardiac
Congestive heart failure
Iatrogenic
Sedative or narcotic overdose

LO-CCHS/HD later-onset central hypoventilation syndrome and hypothalamic dysfunction, *ROHHAD* rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation syndrome

frequent in LO-CCHS, but other mutations can occur. Ten percent of the patients have a non-PARM mutation like a missense, a nonsense or more often a frameshift mutation [1]. In our case series, a PARM 20/25 is the most common mutation in adult-onset CCHS, present in about 80% of all cases. In the past, it was suspected that no mutations larger than 25 repeats were present in adult-onset cases [21]. In this case series, we found a case with a PARM 20/28 mutation as well as a PARM 20/24 mutation and one non-PARM associated with adult-onset CCHS (Fig. 2). Most non-PARM are de novo [9, 21]. It is an autosomal dominant disorder with reduced penetrance in heterozygous PARM up to 25 repeats [2, 8, 18]. Observations argue for a gain-of-function mechanism [8]. Expansions of 26 repeats or higher are considered full-penetrance alleles and asymptomatic carriers may only be found in association with significant degrees of somatic mosaicism [2, 21]. Up to 10(–25)% of unaffected parents show somatic mosaicism for the expansion mutation seen in the child [17, 21]. Therefore, the recurrence risk of healthy individuals carrying an expansion of six repeats can be as high as 50%, depending on the unquantifiable extent of their germline mosaicism. Polyalanine mutations are transmitted unchanged and so are meiotically stable. These mutations have also been found to be mitotically stable [2]. There are cases in which no *PHOX2B* mutations are found. Defects either impairing correct expression or splicing of the gene, or residing outside the transcription unit (position effects) are a possible explanation. Genetic heterogeneity could also explain the non-mutant patients [31]. However, the exact mechanism of inheritance is still unknown. Some mutations in *PHOX2B* can be missed depending on the method for molecular genetic analysis. One could perform PCR amplification of the 20-repeat polyalanine expansion region in exon 3 followed by fragment analysis or PCR amplification of all three coding exons followed by their sequencing. Fragment analysis can detect polyalanine expansion mutations (approximately 90% of *PHOX2B* mutations) and some non-PARMs, whereas sequencing can detect expansion mutations as well as non-PARMs. However, fragment analysis has the advantage of detecting low-level mosaicism, which can be helpful for family studies when the proband is known to have an expansion mutation, and is, therefore, referred to as the *PHOX2B* screening test [11]. Multiple ligation-dependent probe amplification can detect whole gene or exon deletions that are not detected with *PHOX2B* sequencing [32]. A stepwise genetic work-up for *PHOX2B* testing for an individual with central hypoventilation is recommended after excluding other explaining disorders. Fragment analysis is performed first and if this reveals no mutation, a sequencing test is performed. Finally, if no mutation, a multiple ligation-dependent probe amplification test can be performed [13].

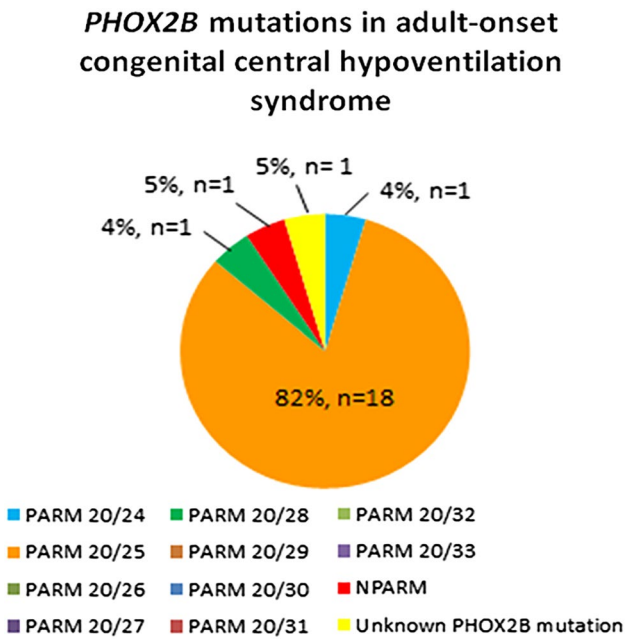

Fig. 2 Frequency of different PHOX2B mutations in adult-onset congenital central hypoventilation syndrome reported in the literature, including the presented case. Most mutations concern a heterozygous PARM of 5 extra alanine residues (PARM 20/25). One patient was reported carrying a 'mild PHOX2B mutation' and is represented as 'unknown PHOX2B mutation'. *PARM* polyalanine repeat expansion mutation, *NPARM* non-PARM

Implications

For the clinical practice

1. Subtle symptoms and signs can be indicative for CCHS during childhood. For example unexplained drug-resistant 'epilepsy', cognitive impairment as sequelae of hypoxemia and hypercapnia, polycythaemia and right ventricular dysfunction [20, 33].
2. As right heart dysfunction can range from mild to life-threatening cor pulmonale careful evaluation is needed. Even CCHS patients with smaller PARMs can have severe right heart failure. Cardiac failure alters peripheral chemoreceptor sensitivity and so reduces capacity to compensate for a blunted central respiratory drive [33].
3. Correct diagnosis is important to reduce complications as hypoxia, desaturations, apnoea, seizures, unplanned intensive care admissions, prolonged hospital stays and long-term need for tracheotomies and ventilation [1].
4. There is an increased risk for sudden infant death syndrome or apparent life-threatening episodes [8].
5. Anaesthesiologists need to be aware of undiagnosed LO-CCHS especially if unexplained postoperative respiratory depression [1]. Other warning signs are a family history of CCHS, past history of unusual prolonged

recovery from sedation or anaesthesia or breathing pauses at relatively lower concentrations of anaesthetics and a significant decrease of oxygen saturation when asleep or in the event of severe respiratory infection [1, 34].
6. Polysomnography in asymptomatic family members of CCHS children is recommended. These individuals can be mutation carriers, either germinal or somatic, and they should be advised on the increased risk of complications associated with respiratory infections or the use of respiratory depressant drugs [18].

For treatment and drug use

1. Progestins stimulate ventilation and enhance chemosensitivity. Increased levels of progesterone during pregnancy do not improve ventilation in CCHS patients. There are anecdotal reports on desogestrel 75 µg to restore chemosensitivity in CCHS possibly due a higher progestin potency value [35].
2. Patients exhibiting only nocturnal hypoventilation should usually be treated with nocturnal non-invasive bilevel positive airway pressure ventilation. The ventilation should be extended to daytime if hypoventilation also develops during daytime. In such cases, combination with diaphragm pacing by phrenic nerve stimulation may be taken into consideration. However, the beneficial effect of diaphragm pacing in these patients is only reported in some cases and has not been studied in controlled trials. For this reason, diaphragm pacing is not an evidence-based recommended practice in CCHS patients. Home mechanical ventilation via tracheostomy is required for younger children for long-term care [34].
3. Anaesthetic techniques should limit respiratory depressant agents and ensure adequate monitoring to detect postoperative apnoeas [1]. Non-opioid or local anaesthetics are preferred. All anaesthetic drugs should be administered by titration to desired effect, preferably using short-acting drugs. One should take into account the risk of inducing ANSD in CCHS patients. For this reason, propofol is not a good choice for the induction of anaesthesia or should be used carefully [34].
4. Patients with CCHS require lifelong mechanical ventilation and do not outgrow the disorder [1].

For genotype–phenotype correlation and genetic counselling

1. PARM 20/25 mutations are not fully penetrant. Longer PARMs containing 26–33 alanine repeats cause typical CCHS and are not associated with variable penetrance or adult-onset presentations, though exceptions exist [8, 20].
2. *PHOX2B* mutations can be in a mosaic state. Patients carrying a mosaic mutation are at risk to develop the disease [8].
3. The phenotype tends to be more severe with longer PARMs and patients with LO-CCHS harbour only the shortest expansions, though exceptions may occur. Even a severe CCHS case of the 20/24 has been reported without detection of an additional non-PARM mutation, although the possibility of mutations in regulatory regions of *PHOX2B* gene or genetic alterations in other genes cannot be excluded [8, 11]. PARM 0/24 or 0/25 present primarily after exposure to respiratory depressants or severe respiratory infection [1].
4. HSCR has been associated with all *PHOX2B* mutations except for PARM 20/25 [34].
5. Non-PARM mutations increase the risk for tumour development. Here also incomplete penetrance and somatic mosaicism were hypothesized, because approximately 5–10% of healthy parents of patients with CCHS were found to harbour a *PHOX2B* mutation [1].
6. Longer PARM size has been associated with severity of autonomic dysfunction (number of ANSD symptoms), increased R-R interval on Holter monitoring, severity of ventilatory dependence and predict the need for cardiac pacemaker [21, 30].
7. The specific *PHOX2B* mutation informs of the severity of hypoventilation and the need for ventilation [1].
8. Parents of CCHS patients should be genetically tested to determine the risk of passing the *PHOX2B* mutation and to assess their own risk of requiring mechanical ventilation [1].
9. The recurrence risk of healthy individuals carrying a PARM 20/60 can be as high as 50%, depending on the unquantifiable extent of their germline mosaicism, a circumstance which has to be taken into account in genetic counselling to families [2].
10. As consequence of the challenging use of PCR in *PHOX2B* mutations, an accurate detection of *PHOX2B* mutations is required to make the diagnosis of CCHS [1, 11, 36].
11. Genetic counselling has become indispensable for couples with an affected child to determine the recurrence risk to a fetus [36].

For pregnancy

1. Pregnancy in CCHS patients carries a high risk that should be managed preferably at tertiary centres [1].
2. In the normal fetus, modest hypercapnia stimulates the amount of time the fetus spends breathing and the respiratory rate, while this is not seen in a fetus with CCHS. The inability of the respiratory centre to respond

to hypercapnia and hypoxemia is inconsequential for the fetus but is potentially lethal after birth [37].
3. The level of ventilatory support may need to be adjusted as pregnancy progresses for example because of an increased respiratory load with enlarging uterus [28].
4. Neonatal support should be available and adequate ventilatory support for a mother with CCHS during labour, partus and post-partum period is indicated [1, 28].
5. Parodi et al. mentioned a case of adult-onset CCHS in a female with diagnosis at the age of 26 years who had two spontaneous abortions [18]. Our case experienced a missed abortion, perhaps due to nocturnal hypoxemia.
6. Genetic counselling and prenatal *PHOX2B* testing for the fetus from a CCHS parent should be offered [1, 13, 37].

For follow-up

1. In PARM 20/24 and 20/25 mutations annual in-hospital comprehensive physiological testing (awake and asleep), exogenous and endogenous gas challenges, autonomic testing, annual neurocognitive assessment and annual 72-h Holter recording and TTE are recommended [28].
2. Infants under the age of 3 years should undergo evaluations every 6 months [28].
3. Patients with non-PARM and longer PARM should also be screened for HSCR [28].
4. Patients with PARM with a repeat length of 28 or more should receive annual imaging to assess for tumours of neural crest origin with chest and abdominal imaging [28].
5. Non-PARM patients should receive abdominal imaging and urine catecholamines every 3 months in the first 2 years, then every 6 months until 7 years of age [28].

Conclusions

Because of the possible deleterious respiratory consequences, adult-onset CCHS is an important differential diagnosis to consider in patients who suffered an episode of central hypoventilation and to be aware of regarding pharmacological therapy in known patients. In case of suspicion, genetic analysis of *PHOX2B* is warranted, given the important implications for the clinical practice.

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Compliance with ethical standards

Conflict of interest There are no competing interests for any author.

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