Congenital Central Hypoventilation Syndrome: Diagnosis and Long-Term Ventilatory Outcomes

Clinical Medicine Insights: Pediatrics
Volume 17: 1–6

DOI: 10.1177/11795565231169556
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ABSTRACT

BACKGROUND: Congenital central hypoventilation syndrome (CCHS), a rare disease caused by variants in the paired-like homeobox 2B (*PHOX2B*) gene, affects regulation of respiration necessitating lifelong assisted ventilation (AV). Most patients require full-time AV during infancy and some patients may sustain adequate spontaneous ventilation during wakefulness and change AV modalities at a later age. The aims of this study were to assess the changes in duration and modalities of AV, long-term respiratory outcomes, and to correlate them with *PHOX2B* genotypes.

METHODS: We conducted a retrospective study of patients with CCHS treated at our institution between January 1997 and May 2022. Results analyzed included: clinical presentation, *PHOX2B* genotype, modality and duration of AV at diagnosis and follow-up, survival, and transition to adult care.

RESULTS: We identified 30 patients with CCHS—8 with *PHOX2B* nonpolyalanine repeat mutations (NPARMs), 21 with polyalanine repeat mutations (PARMs), and 1 with unknown *PHOX2B* genotype. The median age at presentation was 0.25 months (IQR 0.1-0.7 months). At diagnosis of CCHS, 24 (80%) patients required continuous AV and 28 (93%) received AV via tracheostomy. Twenty-six patients required sleep-only AV at a median age of 9 months (IQR 6-14 months). Nine patients requiring sleep-only AV underwent tracheostomy decannulation at a median age of 11.2 years (IQR 5.9-15.7 years) and used noninvasive positive pressure ventilation or diaphragm pacing. There was insufficient evidence to conclude that patients with PARMs and NPARMs differed by age at presentation ($P = .39$), tracheostomy ($P = .06$), and transition to sleep-only AV ($P = .9$). Six patients transitioned to adult care, 23 continued receiving pediatric care, and 1 patient died due to complications from Hirschsprung's disease.

CONCLUSION: Our study demonstrates prolonged survival and good long-term respiratory outcomes possibly related to the early diagnosis of CCHS, optimizing AV strategies, and multidisciplinary care. The increasing number of patients attaining adulthood highlights the necessity for multidisciplinary care for adults with CCHS.

KEYWORDS: Congenital central hypoventilation syndrome, *PHOX2B*, diaphragm pacing, home ventilation, tracheostomy, central sleep apnea

RECEIVED: December 5, 2022. **ACCEPTED:** March 27, 2023.

TYPE: Original Research

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Introduction

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder of the autonomic nervous system caused by variants in the paired-like homeobox 2B (*PHOX2B*) gene.[1,2] The estimated incidence of CCHS is one in 148 000 to 200 000 live births and over 1000 cases have been reported worldwide.[2] Patients with CCHS generally present in the newborn period, have impaired central respiratory control, and lack normal responses to hypoxemia and hypercapnia.[1,3] This results in a variety of clinical manifestations, including apnea, hypoxemia, and hypoventilation, which predominantly manifests during sleep, and in some cases, may persist even during wakefulness.[1,4] Since patients with CCHS lack objective and subjective responses to hypoxemia and hypoventilation, they do not manifest signs of respiratory distress such as nasal flaring, tachypnea, and chest retractions. Therefore, patients require lifelong assisted ventilation (AV) ranging from sleep-only AV to continuous AV.[1,4] Commonly used AV modalities include positive pressure ventilation via tracheostomy (PPV-T), noninvasive positive pressure ventilation (NPPV) such as bilevel positive airway pressure (BPAP), and diaphragm pacing (DP) via phrenic nerve stimulation.[2]

The *PHOX2B* gene contains a repeat sequence of 20 alanines in exon 3. *PHOX2B* variants are classified into a) polyalanine repeat mutations (PARMs) accounting for 90% of CCHS cases and characterized by expansion of the normal 20 alanine repeat sequence in the range of 24 to 33 alanine repeats producing genotypes of 20/24 to 20/33, and b) nonpolyalanine repeat mutations (NPARMs) that are less common (around 10% of CCHS cases), and include frameshift, nonsense, and missense mutations.[1] Generally, there is a correlation between the *PHOX2B* genotype and severity of the phenotype. Compared to patients with PARMs, patients with NPARMs generally have more severe phenotypes requiring continuous AV, a higher incidence of Hirschsprung's disease (HD), and neural crest tumors (NCT).[1,5]

To ensure optimal oxygenation and ventilation, the American Thoracic Society CCHS clinical policy statement recommends PPV-T during early childhood to optimize neurocognitive outcomes.[1] During infancy, most children with CCHS require continuous AV; however, with growth and maturation of the respiratory system, some patients can transition to sleep-only AV and pursue other AV modalities.[6-8] However, there is limited literature on the optimal timing and strategies to attempt transition from continuous to sleep-only AV.[3,4] Moreover, it is unknown if the ability to transition from continuous to sleep-only AV differs based on *PHOX2B* genotypes. Most studies reporting long-term ventilatory outcomes in patients with CCHS were performed over 20 years ago and/or in the pre-*PHOX2B* era without genetic confirmation of CCHS.[6,9,10] With advances in patient management and ventilatory strategies, there is a dearth of literature on the ventilatory outcomes of patients with CCHS. The primary aim of our study was to describe the respiratory clinical features, modalities of AV, and outcomes of patients with CCHS treated at our hospital. The secondary aim of our study was to compare AV modalities and respiratory outcomes based on *PHOX2B* genotypes.

Methods

We conducted a retrospective study of children and young adults with CCHS treated at Children's Healthcare of Atlanta between January 1997 and May 2022. Patients with CCHS were identified by reviewing the medical records of patients treated in the pulmonology and sleep clinics during the study period. De-identified demographic and clinical information was collected for all patients. The recorded and analyzed data included age, age and clinical features at presentation, polysomnography results at diagnosis, age at diagnosis, *PHOX2B* variant, age at tracheostomy, initial mode and duration of AV requirement, age at transition to sleep-only ventilation, age at tracheostomy decannulation (TD), attempts to transition to different modalities of AV, outcomes, and associated clinical features such as HD, cardiac dysrhythmia, pulmonary hypertension, NCT, and neurodevelopmental delays. The study was approved by the Institutional Review Board at Children's Healthcare of Atlanta.

Statistical analysis

Categorical variables were described as frequency and percentage while continuous variables were reported as median and interquartile range (IQR). Comparisons between *PHOX2B* genotypes (PARM vs NPARM) were conducted using Fisher's tests for categorical variables and Wilcoxon rank sum tests for continuous variables. All hypotheses were 2-sided and a *P*-value below .05 was considered significant. Analyses were conducted in R version 4.1.3 (R Foundation for Statistical Computing) with the gtsummary package.[11]

Results

We identified 30 patients with CCHS during the study period. The median age was 13 years (IQR 8-20 years, Table 1). The median duration of follow-up was 11.9 years (IQR 7.3-18.9 years), and the longest duration of follow-up was 22.7 years. There were 21 patients with *PHOX2B* PARMs and 8 patients with NPARMs. *PHOX2B* genotype information was not available for one patient with HD requiring PPV-T during sleep. Patients presented at a median age of 0.25 months (IQR 0.1-0.7 months) with respiratory failure and failure to wean off AV (77%), apnea (60%), hypoxemia (20%), cyanosis (7%), and brief resolved unexplained event (BRUE, 3%). Other symptoms at presentation included poor feeding, seizure, abdominal mass, and obstructive sleep apnea (OSA). The median age at diagnosis was 1.3 months (IQR 0.8-2.3 months). Among 12 patients who underwent polysomnography before confirming the CCHS diagnosis, predominant findings included central sleep apnea (CSA, 83%), sleep-related hypoxemia and hypoventilation (83%), and OSA (67%). Some of the associated clinical features in patients with CCHS included HD (43%), cardiac dysrhythmia requiring cardiac pacemaker implantation (27%), mild neurodevelopmental delays (47%), and NCT (7%). None of the patients had echocardiographic signs of pulmonary hypertension.

At diagnosis, 80% of patients required full-time AV whereas 20% required sleep-only respiratory support (Table 2). Twenty-seven patients underwent tracheostomy at a median age of 1.4 months (IQR 1.1-2.1 months). At the end of the study period, 26 patients required sleep-only AV, and the median age of transition from full-time to sleep-only AV was 9 months (IQR 6-14 months). However, during respiratory infections, several young children who were weaned off AV during wakefulness required continuous AV.

When AV modalities were compared at diagnosis and at the end of the study period, there were fewer patients using PPV-T (63%) and more patients were using NPPV or DP (Table 3). Two patients with NPARMs initially requiring supplemental oxygen only during sleep required initiation of NPPV during sleep due to emergence of sleep-related hypoventilation or worsening central sleep apnea. Utilizing systematic multidisciplinary algorithms, 9 patients requiring sleep-only AV underwent TD at a median age of 11.2 years (IQR 5.9-15.7 years). Five patients aged 11 to 21 years requiring PPV-T only during sleep were unsuccessful in changing AV modalities for potential TD. One patient was unable to use DP due to improper placement of left cervical phrenic nerve electrode resulting in arm pain with DP. Despite systematic multidisciplinary evaluations, 4 patients failed to transition to NPPV due to inability to tolerate interfaces or inability to obtain adequate NPPV settings during polysomnography. The most utilized ventilator modes in patients with PPV-T and NPPV were synchronized intermittent mandatory ventilation pressure-controlled mode and BPAP spontaneous timed modes, respectively.

Table 1. Clinical characteristics of the study population, n = 30.

VARIABLE (N = 30, UNLESS OTHERWISE NOTED)	
Age (years), median (IQR)	13 (8-20)
Gender, *n* (%)	
Female	18 (60%)
Male	12 (40%)
PHOX2B genotype (n = 29),[a] n (%)	
PARM	21 (72%)
20/25	6 (21%)
15/26	1 (3.4%)
20/26	4 (14%)
13/27	1 (3.4%)
20/27	9 (31%)
NPARM	8 (28%)
Symptoms at presentation, n (%)	
Apnea	18 (60%)
Hypoxemia	6 (20%)
Respiratory failure	23 (77%)
Cyanosis	2 (6.7%)
BRUE	1 (3.3%)
Other symptoms[b]	5 (17%)
Age at presentation (months), median (IQR)	0.25 (0.1-0.7)
Polysomnography findings at diagnosis (n = 12), n (%)	
Central sleep apnea	10 (83%)
Obstructive sleep apnea	8 (67%)
Sleep-related hypoxemia	10 (83%)
Sleep-related hypoventilation	10 (83%)
Age at diagnosis (months), median (IQR)	1.3 (0.8-2.3)
Hirschsprung's disease, n (%)	13 (43%)
Cardiac dysrhythmia requiring cardiac pacemaker, n (%)	8 (27%)
Neural crest tumor, n (%)	2 (6.7%)
Neurodevelopmental delay, n (%)	14 (47%)

Abbreviations: BRUE, brief resolved unexplained event; IQR, interquartile range; NPARM, nonpolyalanine repeat mutations; PARM, polyalanine repeat mutations; PHOX2B, paired-like homeobox 2B.
[a]*PHOX2B* genotype information was not available for one patient with Hirschsprung's disease requiring positive pressure ventilation via tracheostomy during sleep. This patient developed respiratory failure at birth with hypoxemia and hypoventilation and was unable to wean from assisted ventilation. There was abdominal distension at birth confirmed by rectal biopsy as Hirschsprung's disease. A clinical diagnosis of congenital central hypoventilation syndrome was made when extensive evaluations showed absence of cardiopulmonary, neurologic, neuromuscular, or metabolic diseases that could explain persistent respiratory failure.
[b]Other symptoms = poor feeding, seizure, abdominal mass (neuroblastoma), obstructive sleep apnea, and sibling of patient with congenital central hypoventilation syndrome.

Patients with NPARMs were significantly younger than those with PARMs ($P = .01$, Table 4). There was insufficient evidence to conclude that age at presentation ($P = .39$), age at tracheostomy ($P = .06$), and age at transition to sleep-only AV ($P = .90$) differed by *PHOX2B* genotypes (PARM vs NPARM). Among 8 patients with *PHOX2B* NPARMs, 6 used PPV-T, and 2 never underwent tracheostomy and used NPPV only during sleep. Compared to patients with PARMs, there was a higher prevalence of HD in patients with NPARM ($P = .04$). There was no significant difference in the presence of NCT ($P = .07$), cardiac dysrhythmia requiring an implanted cardiac pacemaker ($P = .07$), and neurodevelopmental delay ($P = 1.00$) based on *PHOX2B* genotypes. At the end of the study duration, 6 (20%) patients had transitioned to adult care and 23 (77%) continued to receive pediatric care (Table 2). One patient with NPARM died at 4 years of age due to complications from HD.

Discussion

Our study shows that most children with CCHS present in the neonatal period, require continuous AV at the time of diagnosis, utilize PPV-T as the initial modality of AV, and can transition to sleep-only AV later in infancy. Later in childhood, several patients requiring PPV-T only during sleep changed AV modalities to NPPV or DP and underwent TD. Patients with PARMs and NPARMs did not differ based on age at presentation and tracheostomy, and transition to sleep-only AV. Additionally, survival was good, and several patients transitioned to adult care. Our study adds to the growing literature on clinical presentations, survival, and long-term ventilatory outcomes in patients with CCHS and provides a correlation with the *PHOX2B* genotype.

Consistent with prior reports, most patients presented in the neonatal period with respiratory failure and failed liberation from AV, apnea, cyanosis, hypoxemia, and BRUE leading to the diagnosis of CCHS during early infancy.[1,12] However, some patients with the relatively milder *PHOX2B* 20/25 PARM and NPARMs presented later in infancy or during early childhood. Indeed, late-onset CCHS has been reported in patients with *PHOX2B* 20/25 PARM and NPARMs suggesting that clinicians should maintain a high index of suspicion for CCHS even beyond the neonatal period.[1,13,14] Although the typical polysomnographic features of CCHS are hypoventilation, hypoxemia, and CSA that are more severe in nonrapid eye movement sleep than during rapid eye movement sleep, our study reports several patients with OSA without evidence of airway obstruction on endoscopic evaluation.[15] While less common, recent studies have reported OSA during diagnostic polysomnography in some children with CCHS.[14,16-18] Indeed, in a mouse model of CCHS, Madani et al reported obstructive and mixed apneas in newborn mice possibly related to hypoglossal dysgenesis.[19] The hypoglossal nerve maintains pharyngeal patency and upper airway muscle tone.[20] Based on

Table 2. Respiratory clinical features and outcomes of the cohort, n = 30.

VARIABLE (N = 30, UNLESS OTHERWISE NOTED)	
Age at tracheostomy (months),[a] median (IQR)	1.4 (1.1-2.1)
Age at initial hospital discharge (months),[b] median (IQR)	4.0 (3.3-7.2)
Initial duration of AV, n (%)	
Full-time	24 (80%)
Sleep-only	6 (20%)
Age at sleep-only AV (months),[c] median (IQR)	9 (6-14)
Age at tracheostomy decannulation (years),[d] median (IQR)	11.2 (5.9-15.7)
Failed transition from PPV-T,[e] *n* (%)	
Failed DP	1 (20%)
Failed NPPV	4 (80%)
Ventilator mode, n (%)	
SIMV-PC	13 (43%)
SIMV-VC	6 (20%)
AVAPS	1 (3.3%)
BPAP ST	7 (23%)
BPAP T	1 (3.3%)
DP	3 (10%)
Outcome, n (%)	
Death	1 (3.3%)
Ongoing pediatric care	23 (77%)
Transition to adult care	6 (20%)

Abbreviations: AV, assisted ventilation; AVAPS, average volume-assured pressure support; BPAP ST, bilevel positive airway pressure spontaneous timed; BPAP *T*, bilevel positive airway pressure timed; DP, diaphragm pacing; IQR, interquartile range; NPPV, noninvasive positive pressure ventilation; PPV-T, positive pressure ventilation via tracheostomy; SIMV-PC, synchronized intermittent mandatory ventilation pressure controlled; SIMV-VC, synchronized intermittent mandatory ventilation volume controlled.
[a]n = 27. The age at tracheostomy for one patient was not available despite a thorough chart review.
[b]n = 28. The age at initial hospital discharge for 2 patients was not available despite a thorough chart review.
[c]n = 26. One patient died at 4 years of age and required continuous assisted ventilation at the time of death and another patient aged 1 year had not transitioned entirely to sleep-only assisted ventilation at the end of the study. Both patients had *PHOX2B* nonpolyalanine repeat mutations.
[d]n = 9.
[e]n = 5.

the limited literature on OSA in CCHS and our study demonstrating OSA in some patients with CCHS, clinicians interpreting sleep studies in suspected cases of CCHS should become aware of co-existent OSA as one of the associations with CCHS.[14,16,17]

Table 3. Comparison of assisted ventilation modalities.

AV MODALITY	AT DIAGNOSIS, N (%)	CURRENT, N (%)
PPV-T	28 (93%)	19 (63%)
NPPV	0 (0%)	9 (30%)
Diaphragm pacing[a]	0 (0%)	3 (10%)
Oxygen	2 (6.7%)	0 (0%)

Abbreviations: AV, assisted ventilation; NPPV, noninvasive positive pressure ventilation; PPV-T, positive pressure ventilation via tracheostomy.
[a]One patient used PPV-T during sleep and diaphragm pacing for a few hours during the day.

Following an initial period of continuous AV requirement after diagnosis, most patients were able to sustain adequate spontaneous ventilation during wakefulness and remain off AV when awake by around 9 months of age. In a survey study of 196 patients with CCHS, Vanderlaan et al reported that among CCHS children determined to require sleep-only AV, two-thirds of children were able to maintain adequate ventilation off AV during wakefulness by 12 months of age.[8] Other studies have reported that children with CCHS had adequate spontaneous ventilation when awake between birth and 10 months of age.[6,8,10] This improvement is likely due to maturation of the respiratory system rather than an improvement in ventilatory control in CCHS, and it is important for clinicians to recognize that the need for AV during sleep will be lifelong.[6,7] Based on the American Thoracic Society CCHS clinical policy statement, following the diagnosis of CCHS in early infancy, most patients underwent tracheostomy for ventilation access.[1] However, some patients with a later diagnosis of CCHS or atypical presentations used NPPV when they developed hypoventilation or severe CSA. Studies have reported infants with CCHS treated only with NPPV since birth highlighting differences in medical practices and AV modalities between different countries.[8,21,22]

Later in childhood, several patients requiring sleep-only AV sought TD by pursuing different modalities of AV such as NPPV and DP. AV modalities and changes to different modalities of AV should be individualized for each patient based on the duration of AV dependence, age, risks and benefits of different AV forms, and the patient's wishes.[2] Vanderlaan et al reported that approximately 50% of children changed AV modalities around 6 to 11 years of age for increased portability and removal of the tracheostomy tube.[8] In our study, the median age at TD was similar to a recent study of 22 children with CCHS reporting the mean age at TD of approximately 10 years.[12]

Like other studies, based on *PHOX2B* genotypes, PARMs were most prevalent in our study.[5,12] However, there was a relatively higher proportion of patients with NPARMs in our cohort in contrast to other studies reporting NPARMs in approximately 10% of all CCHS cases.[1,5] This may be due to

Table 4. Comparisons based on *PHOX2B* genotypes.

VARIABLE	NPARM (N=8, UNLESS OTHERWISE NOTED)[A]	PARM (N=21, UNLESS OTHERWISE NOTED)[A]	*P* VALUE[B]
Age (years)	6 (2-9)	16 (11-20)	.01
Age at presentation (months)	0.6 (0.3-0.88)	0.2 (0.1-0.6)	.39
Age at tracheostomy (months)	2.1 (1.9-2.8); n=6	1.3 (1-1.9); n=20[c]	.06
Age at sleep-only AV (months)	8.3 (6.6-10); n=6[d]	8.1 (5.3-13.2); n=19[e]	.90
Age at tracheostomy decannulation (years)	NA	11.2 (5.9-15.7); n=9	NA
Hirschsprung's disease	6 (75%)	6 (29%)	.04
Cardiac dysrhythmia requiring cardiac pacemaker	0 (0%)	8 (38%)	.07
Neural crest tumor	2 (25%)	0 (0%)	.07
Neurodevelopmental delay	4 (50%)	9 (43%)	1.00

Abbreviations: AV, assisted ventilation; NA, not applicable; NPARM, nonpolyalanine repeat mutations; PARM, polyalanine repeat mutations; PHOX2B, paired-like homeobox 2B.
[a]Median (interquartile range) or n (%).
[b]Wilcoxon rank sum test and Fisher's exact tests.
[c]The age at tracheostomy for one patient with *PHOX2B* 20/27 PARM was not available.
[d]One patient died at 4 years of age and required continuous assisted ventilation at the time of death and another patient aged 1 year had not transitioned entirely to sleep-only assisted ventilation at the end of the study.
[e]The age at sleep-only assisted ventilation was not available for one patient with *PHOX2B* 20/27 PARM.

increased awareness of the variable phenotypes and atypical presentations in patients with NPARMs and availability of *PHOX2B* genetic tests.[14] In our study, patients with PARMs and NPARMs did not differ in age of presentation, tracheostomy, or transition to sleep-only AV. Despite the typical association of NPARMs with severe respiratory phenotypes requiring continuous AV, only 2 patients with NPARMs required continuous PPV-T.[1,5] Furthermore, 2 patients with NPARMs initially requiring oxygen only during sleep later developed hypoventilation or severe CSA requiring initiation of NPPV during sleep and never underwent tracheostomy. This highlights the importance of formulating an individualized plan of care and performing periodic polysomnography to detect the emergence of respiratory control abnormalities.[14] Among 6 patients with NPARMs using sleep-only PPV-T, none underwent TD. While this could be due to the association of NPARMs with severe phenotypes consistent with previous reports, it may also be attributed to the relatively younger age of patients with NPARMs compared to patients with PARMs, who underwent TD at a median age of 11 years.

Overall, we found good long-term respiratory outcomes and prolonged survival in patients with CCHS with only one death due to complications of HD. Previous studies described substantial mortality in children with CCHS due to cor pulmonale, aspiration, pneumonia, sepsis, cardiac arrest, and respiratory depression due to alcohol abuse.[9,10,23] Pulmonary hypertension, reported as prevalent in children with CCHS due to suboptimal AV, undetected recurrent hypoxemia and hypoventilation, was not seen in our patients.[9] This could be due to the early diagnosis of CCHS in our cohort, advances in management strategies based on CCHS guidelines, and periodic cardiorespiratory evaluations to determine the ventilatory requirement of patients and optimization of ventilator settings.[1,2,24] Since advances in CCHS diagnosis and management have led to prolonged survival, an increasing number of children are transitioning to adult care necessitating high-quality multidisciplinary programs for adults with CCHS.[4,25]

Our study is limited by a single-center retrospective study design with a relatively small sample size. Patients in our study had relatively milder respiratory phenotypes requiring sleep-only AV which may not be representative of patients with more severe respiratory phenotypes. Additionally, our study may have missed patients such as those who died early in life before the diagnosis of CCHS was ascertained and older children (late-onset CCHS) who were yet to be diagnosed with CCHS or misdiagnosed as OSA. Despite these limitations, our study demonstrates prolonged survival and good long-term respiratory outcomes possibly due to the earlier diagnosis of CCHS, vigilant management of AV, and multidisciplinary care.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board at Children's Healthcare of Atlanta (IRB#00001357). The requirement for informed consent, parental permission, and assent were waived for this study by the Institutional Review Board at Children's Healthcare of Atlanta.

Consent for publication

Not applicable.

Author contributions

Mary Ellen Fain: Data curation; Investigation; Methodology; Visualization; Writing—original draft; Writing—review & editing. Adrianna L Westbrook: Formal analysis; Investigation; Validation; Visualization; Writing—review & editing. Ajay S Kasi: Conceptualization; Data curation; Investigation; Methodology; Project administration; Supervision; Writing—original draft; Writing—review & editing.

Acknowledgements

We acknowledge the support of the Children's Healthcare of Atlanta and Emory Department of Pediatrics Biostatistics Core. We thank the patients for participating in this study.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

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