

Avoidance of Tracheostomy in a Newborn of Congenital Central Hypoventilation Syndrome

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Abstract

We experienced a term male neonate who required respiratory support soon after birth. Information on his brother aged 156 months at that time with clinically diagnosed Congenital central hypoventilation syndrome (CCHS) and respiratory support by noninvasive ventilation (NIV) since 103 months old prompted us to perform genetic testing. An early diagnosis of moderate type CCHS with genetic test in this patient and his brother in addition to demand of the patient's family encouraged us to continue NIV and avoid tracheostomy in this patient. The patient aged 45 months with Developmental Quotient (DQ) of 83 managed to do well requiring nocturnal NIV alone. This patient had never required an emergent admission to the hospital for respiratory problems, while his brother aged 203 months required it 16 times and once before and after the NIV, respectively. Thus, the NIV appeared to reduce the risk of emergent admission to the hospital. This conveyed great satisfaction in their family.

Keywords: Apnea; Congenital central hypoventilation syndrome; Noninvasive ventilation; PHOX2B mutations; Tracheostomy

birth in whom tracheostomy was avoided with the aid of genotype information in addition to family's demand and cooperation.

Introduction

Congenital central hypoventilation syndrome (OMIM #209880; CCHS) is a disorder of breathing derived from aberrant autonomic control and is characterized by alveolar hypoventilation during sleep. CCHS is extremely rare, with an estimated prevalence of one per 200000 births in France [1]. The diagnosis of CCHS is established based on clinical findings of alveolar hypoventilation and autonomic nervous system dysregulation in the absence of primary pulmonary, cardiac, inherited metabolic disease, congenital malformation, neuromuscular disease, or a causative brain stem lesion that can account for the entire phenotype. Therefore, such newborns undiagnosed with CCHS have usually remained ventilator dependent and been candidates for tracheostomy. Although the tracheostomy with tracheal intubation is the safest way with respect to life support and useful for long-term stable ventilation, a long-term tracheostomy during infancy has some drawbacks such as delayed speech and language development [2], repeated infections in the lower respiratory tract, tracheal granulations and stenosis, cannula obstruction and accidental decannulation, and limitation of daily activity. Therefore, early transition from mechanical ventilation to noninvasive ventilation (NIV) has been advocated and was shown to be successful in some patients by some investigators [3,4].

The recent discovery of a genetic abnormality responsible for more than 90% of CCHS cases enables early diagnosis of CCHS, and the severity of CCHS may be predicted by its genotype [5]. This may increase the possibility of avoiding tracheostomy in infants with CCHS. Here, we report a neonate with suspected CCHS soon after

Case Report

A male patient (patient A) born by cesarean section at 38 weeks of gestation, weighing 2876 g with Apgar scores of 6 and 7 at 1 and 5 min, respectively was admitted to our hospital soon after birth for apnea. His mother had two other sons; his eldest brother (patient B) aged 156 months at that time with clinically diagnosed CCHS had been supported in respiration on tracheostomy until 103 months old and by NIV thereafter (Table 1). Genetic testing performed after birth in patient A and his family members revealed that both patients A and B were heterozygous for *PHOX2B* exon 3 polyalanine repeat expansion mutation, with genotype 20/26 (the normal genotype is referred to as 20/20). His mother showed 53.8% somatic mosaicism with genotype 20/26. The parents wanted to avoid tracheostomy in patient A based on their previous experiences in patient B; the patient B on tracheostomy failed transition to NIV at 2 years old and required 16-times emergent admissions to hospital (2.0 ± 1.6 times/year, 10.6 ± 9.1 - day stay/admission) for cor pulmonale and lower respiratory tract infections until successful transition to NIV at 103 months old, but only once (only 1-day stay) after the NIV. As the genotype 20/26 of *PHOX2B* was considered as moderate type, we managed to continue the 24-h NIV in the patient A using nasal directional positive airway pressure followed by Infant Flow SiPAP System (CareFusion 207, Inc. DBA CareFusion, Palm Springs, CA, USA) (FiO₂, 0.25; peak inspiratory pressure, 10 cm H₂O; positive end-expiratory pressure, 4 cm H₂O; respiratory rate [RR], 40 /min). However, CO₂ retention up to TcpCO₂ of 60 mmHg with sufficient oxygenation and pH of 7.25-7.30 occurred. Subsequent VIVO 40 (Breas Medical AB, Molnlycke, Sweden) with infant mask system (HAROL S.r.l, Milan,

Italy) (Figure 1) (inspiratory positive airway pressure [IPAP], 10 cm H₂O; expiratory positive airway pressure [EPAP], 4 cm H₂O; RR, 40/min) from postnatal day 14 promised adequate ventilation bringing TcpCO₂ to 30 – 50 mmHg. Brain magnetic resonance imaging was unremarkable on postnatal day 33 in this patient A. Although the patient A required transient tracheal intubation and mechanical ventilation for 72 days, due to frequent breath-holding spells starting on postnatal day 60, he required 24-h NIV again followed by NIV support only while sleeping one week after extubation. Hirschsprung's disease with short segment was successfully treated surgically during the period of invasive mechanical ventilation in this patient A. The patient A left hospital on postnatal day 186.



Figure 1: Infant mask system (HAROL S.r.l, Milan, Italy) applied on postnatal day 14 in our patient.

No severe breath-holding spells occurred at home and the respiration was fairly well in patient A; he exhibited TcpCO₂ of 40s mmHg and 40s - 55 mmHg while awake and asleep, respectively during the monitoring at 13 months old, CO₂ retention up to pCO₂ of 66 mmHg and pH 7.28 in the venous blood while crying at 37 months old, required nocturnal NIV alone (IPAP, 18 cm H₂O; EPAP, 4 cm H₂O; RR, 30/min) at 45 months old, and had never required an emergent admission to the hospital for problems associated with respiration. The patient B with nocturnal NIV since 103 months old exhibited TcpCO₂ of 50s mmHg and 40s mmHg while awake and asleep, respectively during the monitoring at 143 months old, and pCO₂ of 68 mmHg and pH 7.31 in the venous blood soon after breath-holding at 192 months old. The patient A exhibited a Tanaka-Binet test Intelligence Quotient (IQ) of 75 at 43 months old, but Enjyoi-shiki Developmental Quotient (DQ) of 83 at 45 months old and appeared to exhibit better motor, linguistic, and mental development compared with patient B who used to understand only some words pronouncing only “ma-ma” or “da-da” at 3 years old. The patient A was scheduled to have surgery for orthodontic problems. The patient B

aged 16 years enjoyed sometimes playing soccer, but suffered from difficulties in pronunciation with hoarse voice and mild mental retardation.

	Patient A	Patient B (eldest brother of patient A)
Age	3 years 10 months	16 years 11 months
Clinical diagnosis	0 days old	21 days old
Genetic diagnosis PHOX2B genotype	33 days old	13 years old
	20/26 polyalanine repeat expansion mutation	20/26 polyalanine repeat expansion mutation
Complications	Hirschsprung's disease (short segmental type)	Hirschsprung's disease (long segmental type)
	Breath-holding spells	Esotropia
Ventilatory support	NIV	Mechanical ventilation on tracheostomy from 28 days old until 8 years 7 months
Emergent admission to hospital for respiratory problems	none	2.0 ± 1.6 times/year and 10.6 ± 9.1- day stay/admission before NIV; once (only one-day stay) after NIV
Respiration (TcpCO ₂)		
Awake without NIV	40s mmHg	50s mmHg
While sleeping with NIV	40s-55 mmHg	40s mmHg
Development	IQ of 75 at 43 months	Mild mental retardation
	DQ of 83 at 45 months	

Table 1: Comparison of patient A with B.

Discussion

The present case managed to avoid tracheostomy based on genetic test results in addition to family's demand and cooperation. This case suggested that tracheostomy is not necessarily required in some patients with CCHS, consistent with previous reports documenting a total of less than 50 CCHS patients with avoidance of tracheostomy [3,6-9].

Our continued NIV and persistent avoidance of tracheostomy were encouraged by the results of genetic testing indicating that the patient was heterozygous for PHOX2B genotype 20/26. Genetic testing facilitates not only prompt diagnosis of CCHS, avoiding the delay for differential diagnosis, but also prediction of the feasibility of avoiding tracheostomy. PHOX2B genotype is closely correlated to the severity of CCHS [5]. Specifically, individuals with the 20/25 genotype rarely require 24-h ventilatory support, those with the 20/26 genotype have variable waking needs depending on the level of activity, and those with genotypes from 20/27 to 20/33 typically require continuous 24-h ventilatory support [5]. Therefore, we considered that the avoidance of tracheostomy was feasible in this patient with genotype 20/26, although we considered the family's demand as well.

Insufficient ventilation and oxygenation during use of NIV is a concern. We carefully monitored O₂ saturation at home during the use of NIV as respiratory support in this patient. The CO₂ retention was monitored during scheduled admissions to the hospital for checking the respiration. Although both patients A and B on NIV sometimes exhibited CO₂ retention showing TcpCO₂ ≥ 45 mmHg, their oxygenation was consistently good. Their parents wanted to continue NIV in the patient A based on experiences in patient B on tracheostomy even after extensive discussion about risks and benefits associated with NIV. An epidemiological survey on 196 patients registered at the CCHS Family Network in the USA and Europe between October 2001 and February 2002 indicated that 28 patients (14%) were never tracheostomized [4]. The American Thoracic Society recommends positive pressure ventilation via tracheostomy in the first 6 – 8 years of life to ensure optimal oxygenation and optimal neurocognitive outcome in patients with CCHS [10]. However, they acknowledge “the authors of this statement believe that positive pressure ventilation via tracheostomy in the first 6 to 8 years of life is associated with better oxygenation, and thus better neurologic development and function, than the use of noninvasive techniques early in life. However, this is not based on high quality evidence, so a scientific study of this hypothesis is recommended” [10]. Ramesh et al. succeeded in establishing NIV for six infants with CCHS at a median age of 8 weeks (range, 5 – 26 weeks) [3]. The three prerequisites proposed for NIV in CCHS candidates are cooperation with NIV, need for respiratory support only while asleep, and good ventilation and oxygenation with NIV fulfilling both TcpCO₂ of 30-45 mmHg and SpO₂ > 95% under room air [10].

With regard to linguistic development in comparison of two brothers with the same CCHS genotype, the NIV appeared to be superior to the stable and safe ventilatory support on tracheostomy. The patient A developed normally at age of 45 months, while the

patient B on tracheostomy until age of 103 months had mental retardation. Suboptimal school performance and/or decreased intellectual function have been observed in CCHS patients [10] and it is unclear whether this is due to hypoxemia or hypercapnia from inadequate ventilatory support or a direct result of the primary neurologic problem associated with CCHS [10]. Although CO₂ retention occurred sometimes, TcpCO₂ were mostly 40s mmHg with good oxygenation in both patients A and B.

Despite its advantages, the use of mask ventilation in young children over a long period may result in some problems, including disruption of facial skin, and impairment of facial growth resulting in mid-face hypoplasia and dental malocclusion. Therefore, they should be strictly reviewed by pediatric plastic surgeons and orthodontists to avoid facial deformities (Table 2) [3,10]. Indeed, flattening of the nose and dental malocclusion were seen in patient A, and the deformities will require surgical repair in future. In addition, patients may require controlled ventilation with tracheal intubation during acute respiratory illnesses and hypercapnia [10].

Conclusion

We reported management of an infant with CCHS in whom NIV applied soon after birth and genotype information regarding CCHS and family’s demand and cooperation managed to avoid tracheostomy. This case suggested that tracheostomy can be avoidable in some patients with well-trained parents regarding the respiratory support, parents’ cooperation, and polyalanine repeat mutation genotype at 20/26. The NIV appeared to reduce burden associated with home medical care, including airway maintenance and body hygiene in their family and the risk of emergent admission to the hospital in both patients A and B. This conveyed great satisfaction in their family.

	Noninvasive ventilation (NIV)	Tracheostomy
Advantages	No surgical procedure	Stable ventilation
	Low risk of respiratory tract infection	Sufficient power for life support
	Little effect on speech and language development	
Disadvantages	Insufficient power for life support (may be life-threatening)	High risk of respiratory tract infection
	Unstable ventilation, especially in acute respiratory illness	Heavy burden for care givers in maintaining airway functioning, including cannula exchange, airway suction, and responses to eventual cannula obstruction and decannulation
	Midfacial hypoplasia	Tracheal granulations and stenosis
	Cosmetic problems derived from redness, marking of facial skin	More limitation of daily activity, including bathing and swimming
		Delayed speech and language development

Table 2: Possible advantages and disadvantages associated with NIV and tracheostomy for long term respiratory support in CCHS.

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Informed consent

Written informed consent was obtained from the patient’s parents for publication of this case report and accompanying images.

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