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A Case of Congenital Central Hypoventilation Syndrome with a Novel Mutation of the *PHOX2B* Gene Presenting as Central Sleep Apnea

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CASE REPORTS

Congenital central hypoventilation syndrome (CCHS) is a rare disease characterized by abnormal autonomic control of breathing resulting in hypoventilation. We report an infant girl with CCHS who presented with central sleep apnea, which was first demonstrated by polysomnography when the infant was 5 months old. She was heterozygous for the novel 590delG mutation of *PHOX2B,* which is classified as a non-polyalanine repeat mutation (NPARM). This mutation is considered to be associated with a relatively mild phenotype.

Keywords: Central sleep apnea, congenital central hypoventilation syndrome (CCHS), PHOX2B

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Congenital central hypoventilation syndrome (CCHS), which was first described by Mellins et al. in 1970, is a rare congenital disease characterized by hypoventilation.[1] Amiel et al., Sasaki el al., and Weese-Mayer et al. identified the paired-like homeobox 2B (*PHOX2B*) gene mutation in CCHS patients.[2-4] Subsequently, Weese-Mayer and colleagues identified mutations in exon 3 of the *PHOX2B* gene in all patients with the CCHS phenotype.[5] Currently, identification of a *PHOX2B* mutation is required to confirm the diagnosis of CCHS. CCHS patients characteristically demonstrate alveolar hypoventilation with diminutive tidal volumes and monotonous respiratory rates during sleep, and in severe cases, also during wakefulness.[5] Affected individuals have diffuse autonomic nervous system dysregulation (ANSD), with anatomical manifestations such as the risk of tumor development. Mcconville et al. identified two *PHOX2B* mutations (600delC, a frameshift mutation and G197D, a missense mutation) as a rare cause of non-syndromic neuroblastoma, which indicates that the underlying *PHOX2B* mutational mechanism influences the risk of tumor and suggests that the position of missense mutations may influence the resulting phenotype.[6]

We report an infant with CCHS who presented with central sleep apnea, which was first demonstrated by polysomnography (PSG) when the infant was 5 months old. She was heterozygous for the novel 590delG mutation of *PHOX2B*.

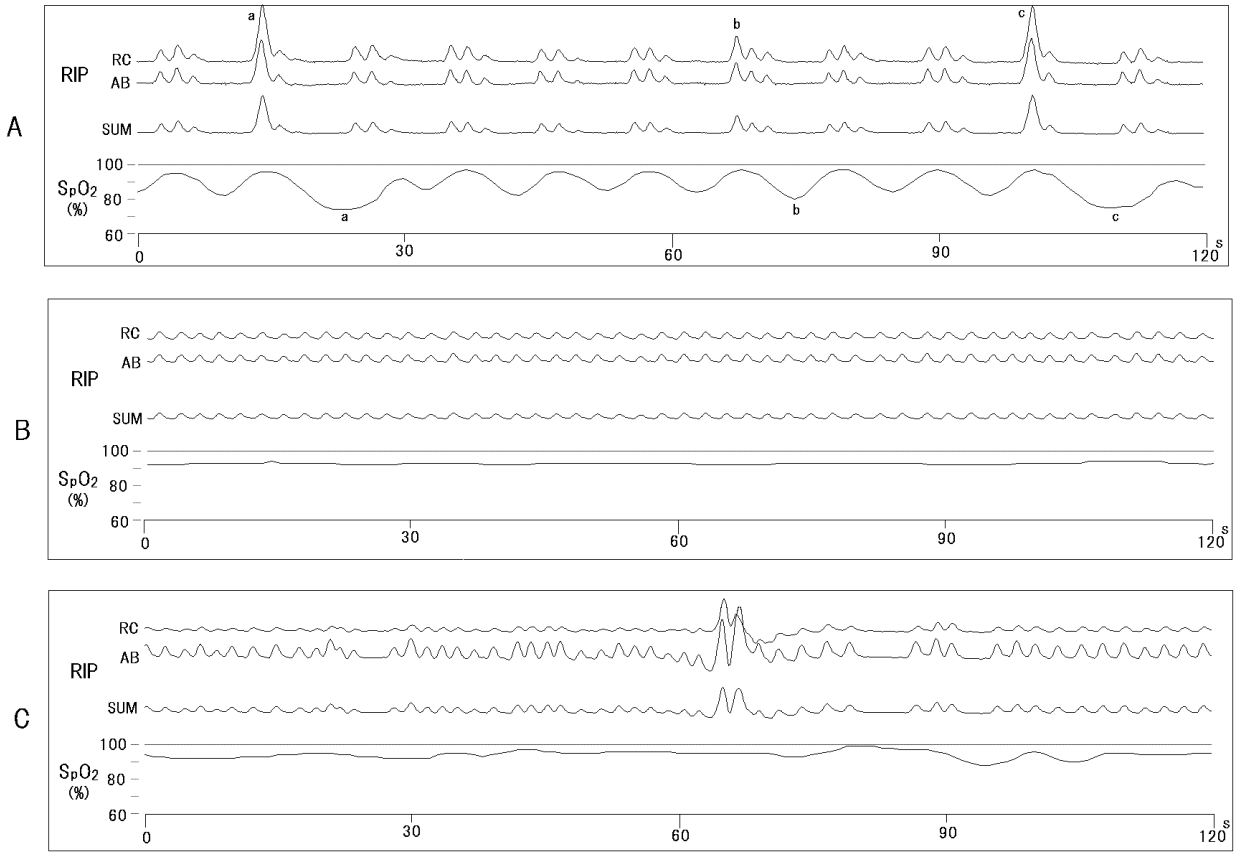
REPORT OF CASE

The patient was a 5-month-old girl delivered by Cesarean section performed for obstructed labor at 40 weeks of gestation without any other complication during pregnancy and delivery. The Apgar scores were 8 at 1 min and 9 at 5 min. She was born to healthy parents without consanguinity: a 33-year-old father and a 23-year-old mother. No relatives of either parent suffered from sleep disorders. Three of the infant's grandparents had undergone surgery under anesthesia without any problems of respiratory management. Neither the parents nor the siblings showed any signs of Hirschsprung disease, tumors of neural crest origin, or other symptoms suggestive of ANSD.

The patient was admitted to NICU because of frequent episodes of respiratory arrest for a few seconds at the onset of sleep on the day of birth. There were no rales or heart murmurs. The muscle tone was good. Venous blood gas analysis revealed a $PvCO_2$ of 32.7 mm Hg in room air. There were no abnormalities on x-ray examination of the chest/abdomen, examination of the cerebrospinal fluid, or ultrasound examination of the brain and heart. The patient was discharged from the NICU one month after birth under home oxygen therapy; supplemental oxygen by nasal cannula (2 L/m) during sleep with SpO_2 monitoring was prescribed at discharge. She was brought to the hospital in which she was born at 5 months of age with a history of frequent episodes of apnea and hypoxemia (lowest $SpO_2 \approx 70\%$) observed during sleep, and was hospitalized at the Fukuoka National Hospital for investigation of the etiology of her condition.

Initial vital signs at admission revealed an SpO_2 of 96% (room air), pulse rate of 134 beats/min, respiratory rate of 34/min, and body temperature of 36.0°C. Physical examination was unremarkable; the color and tone were good. Arterial blood gas analysis was normal (SaO_2 96.2%, PaO_2 85.2 mm Hg, $PaCO_2$ 44.0 mm Hg, HCO_3^- 25.4 mmol/L, and pH 7.379) while awake in room air. The complete blood cell count and blood chemistry profile were within normal limits. There were no abnormalities on chest x-ray, ultrasound examination of heart, abdomen or brain, electrocardiogram, laryngoscopy, electroencephalogram, brain MRI, or examination of vanillylmandelic acid (VMA)/

Figure 1—Representative traces of the respiratory pattern during sleep.



SpO_2 was measured with a toe probe. Therefore, there is a lag time between change in RIP signal and change in SpO_2 (≈ 10s). **(A)** NREM sleep. Frequent central apnea episodes are seen. Marked increase in tidal volume associated with profound desaturation was observed (a-c). **(B)** NREM slow wave sleep. Regular breathing pattern is seen. The SpO_2 is slightly reduced. **(C)** REM sleep. Irregular breathing and sporadic central apnea episodes are seen.

homovanillic acid (HVA) excretion in the urine. These results suggested the absence of any primary pulmonary, cardiac, or neuromuscular disease, or brainstem disorder.

Diagnostic PSG was performed without supplemental oxygen administration. The PSG revealed almost normal sleep architecture except for relatively frequent awakenings during night. The respiratory signals showed frequent central apnea episodes, with an apnea-hypopnea index (AHI) of 161/h. The mean apnea duration of the central apnea episodes was 5 s (range 3-24 s). The apnea events caused recurrent SpO_2 drops without associated arousal response. The lowest SpO_2 recorded was 45%. The frequency of central apnea episodes was greater during NREM sleep than during REM sleep (178/h vs. 96/h). During NREM sleep, the frequency of central apnea episodes and desaturation were the severest at sleep onset (**Figure 1A**), becoming milder as time went by. There were also stable NREM slow wave sleep periods with a regular respiratory rhythm and a slightly reduced oxygen saturation level (SpO_2 91% to 93%) (**Figure 1B**), suggesting the existence of only mild hypoventilation. The mean SpO_2 during PSG was 93.2%.

Genetic study was performed using peripheral blood cells. On amplification and sequencing of the *PHOX2B* gene, heterozygosity for a novel 590delG mutation of *PHOX2B* was detected; on this basis, the infant was diagnosed as having CCHS. Although we recommended a genetic study of the patient's family, only the patient's mother gave consent for such a study, which yielded a normal result.

We introduced noninvasive positive pressure ventilation (NIPPV) for the treatment of central sleep apnea. The initial settings for the NIPPV were: inspiratory positive airway pressure (IPAP) 8 cm H_2O, expiratory positive airway pressure (EPAP) 4 cm H_2O, respiratory rate (RR) 20 breaths/min, inspiration time 0.6 seconds. PSG under NIPPV revealed a marked decrease in the frequency of the central apnea episodes; the AHI was 10.5 and the mean SpO_2 during the PSG was 98.0%. The mean apnea duration was 7 s (range 4-12 s). The lowest SpO_2 recorded was 85%. However, three-fourths of the apnea-hypopnea episodes were classified as obstructive or mixed type, indicating inadequate NIPPV settings. Therefore, the pressure setting was increased.

DISCUSSION

We report a case of CCHS presenting as severe central sleep apnea with a novel mutation of the *PHOX2B* gene. Previous studies have reported various types of *PHOX2B* gene mutations in patients with CCHS. The present case had a novel mutation, namely, a 590delG mutation, of the *PHOX2B* gene.

It is reported that central sleep apnea is a relatively common phenomenon in normal infants.[7] However, the frequency of

central apnea events in this case was extremely high, suggestive of an unusual etiology, which was the reason for our considering genetic testing for CCHS.

PHOX2B is the disease-defining gene for CCHS. Approximately 90% of individuals with the CCHS phenotype are heterozygous for a polyalanine repeat expansion mutation (PARM), and the remaining approximately 10% of individuals with CCHS are heterozygous for a non-PARM (NPARM) (including missense, nonsense, and frameshift mutation) in the *PHOX2B* gene.[5] In this case, 590delG, a frameshift mutation (NPARM), was found in exon 3 of the *PHOX2B* gene. In contrast to the PARMs, the majority of NPARMs occur *de novo* and are associated with very severe phenotypes, including Hirschsprung disease with extensive gut involvement, need for continuous ventilatory support, and increased tumor risk.[5] Most NPARMs are considered to act in a dominant-negative and gain-of-function manner and to be associated with severe phenotypes. However, at present, our patient does not have any severe complications, except the need for ventilatory support during sleep. A few similarly located frameshift mutations (618delC, 577delG) were detected in families with milder phenotypes showing variable penetrance.[8] The 590delG mutation is expected to produce p.G197Afs*111, which may have a milder pathogenic effect than other NPARMs. We could not confirm the penetrance because the father refused to provide a specimen.

CCHS patients usually present with hypoventilation and hypoxemia. They lack both the hypercapnic ventilatory response and hypoxic ventilatory response.[9,10] In this case, while the central sleep apnea was severe, the hypoventilation seemed relatively mild, even during sleep. Although we did not perform tests for ventilatory responses, we think that the patient had a relatively preserved ventilatory response to hypercapnia or hypoxia, because she showed repetitive short desaturation-resaturation cycles, and not sustained severe desaturation during sleep. Moreover, the patient responded to severe desaturation with marked increase in the tidal volume, which also suggested preserved ventilatory responses. These observations and the presumably normal ventilatory control in the awake state, suggested by the normal $PaCO_2$, indicate that the degree of hypoventilation in this patient was considerably mild in the spectrum of CCHS. This notion was also supported by the absence of overt respiratory arrest in the first 5 months of life in the absence of any ventilatory support. We speculate that the incompletely preserved ventilatory response was the reason why this patient presented with central sleep apnea rather than severe hypoventilation.

Although positive pressure ventilation via tracheostomy is recommended during the first several years of life when brain growth and development requiring normoxia occurs,[5] we selected NIPPV for the treatment of central apnea because of the family's strong desire to avoid tracheostomy and the above-mentioned relatively preserved ventilatory responses. However, there are a few risks associated with this line of management that should be borne in mind during the follow-up period: the risk of development of mid-face hypoplasia and the uncertainty of prevention of central apnea.[5] Therefore, careful follow-up of the respiratory status and also monitoring for possible complications of NIPPV as well as emergence of neural crest tumor.[5]

This case had a novel mutation of *PHOX2B* NPARM, and suggested that the severe central sleep apnea is a phenotype of this genotype. This case experience suggests that children with severe central sleep apnea need not only neurological examination, but also genetic testing for mutations of the *PHOX2B* gene.

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DISCLOSURE STATEMENT

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