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CASE REPORTS/CASE SERIES

Late onset congenital central hypoventilation syndrome after exposure to general anesthesia

Syndrome d'hypoventilation alvéolaire centrale congénitale à début retardé après exposition à une anesthésie générale

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Abstract

Purpose *Prolonged postoperative hypoventilation presents a challenge to anesthesiologists with regard to assessing etiology and related treatment. We present a case of recurrent episodes of postoperative hypoventilation in a previously asymptomatic child after uneventful general anesthesia. In this case, the child eventually required lifelong ventilatory support during sleep.*

Clinical features *A case of postoperative hypoventilation in a previously asymptomatic six-year-old child was investigated to determine the possible etiology. After uneventful general anesthesia for dental surgery, the child experienced recurrent episodes of hypoventilation associated with sleep. The child's lungs were mechanically ventilated due to failure of all trials of weaning. Clinical examination was unremarkable and laboratory investigations excluded the possibility of thyroid, hepatic, renal, and neuromuscular diseases. Computerized tomography, magnetic resonance imaging, and electroencephalogram studies were within normal limits. A negative pyridostigmine trial ruled out myasthenia. The child was finally diagnosed as having "late onset congenital central hypoventilation syndrome". Genetic testing revealed a PHOX2B mutation consistent with this diagnosis. The child was discharged home on mechanical ventilatory support during sleep.*

Conclusion *Congenital central hypoventilation syndrome is a rare lifelong multisystem disorder which may occur during the neonatal period as a result of severe genetic mutation in the PHOX2B gene. In mild mutations, a triggering factor, such as sedation or anesthesia, may be required for the syndrome to manifest itself. These patients often require lifelong mechanical ventilatory support, particularly during sleep.*

Résumé

Objectif *Pour les anesthésiologistes, il est difficile d'évaluer l'étiologie de l'hypoventilation postopératoire prolongée et le traitement qui lui est associé. Nous présentons ici un cas d'épisodes récurrents d'hypoventilation postopératoire chez un enfant auparavant asymptomatique après une anesthésie générale sans incident. Dans ce cas, l'enfant a, en fin de compte, requis un soutien respiratoire à vie pendant son sommeil.*

Éléments cliniques *Un cas d'hypoventilation postopératoire chez un enfant de six ans auparavant asymptomatique a été étudié afin d'en déterminer l'étiologie possible. Après une anesthésie générale sans incident pour une chirurgie dentaire, l'enfant a manifesté des épisodes répétés d'hypoventilation associés au sommeil. Les poumons de l'enfant ont été ventilés mécaniquement en raison de l'échec de toutes les tentatives de sevrage. L'examen clinique n'a pas montré d'éléments inusités et les examens de laboratoire ont écarté la possibilité de maladies thyroïdiennes, hépatiques, rénales ou neuromusculaires. Les examens par tomodensitométrie, imagerie par résonance magnétique et électroencéphalogramme étaient dans les limites normales. Grâce à la réalisation d'un test à la pyridostigmine, dont les résultats étaient négatifs, on a pu exclure une myasthénie. Finalement, un diagnostic de « syndrome d'hypoventilation alvéolaire centrale congénitale à début retardé » a été établi chez l'enfant. Des tests génétiques ont révélé une mutation au niveau du PHOX2B, concordant avec ce diagnostic. L'enfant a reçu*

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son congé avec un soutien respiratoire mécanique pendant le sommeil.

Conclusion *Le syndrome d'hypoventilation alvéolaire centrale congénitale est un trouble multisystémique rare et à vie qui peut survenir en période néonatale en raison d'une mutation génétique grave du gène PHOX2B. Dans les mutations plus légères, un facteur déclencheur, comme la sédation ou l'anesthésie, peut être nécessaire pour que le syndrome se manifeste. Ces patients nécessitent souvent un soutien respiratoire mécanique à vie, particulièrement pendant le sommeil.*

Postoperative hypoventilation after general anesthesia is not an uncommon complication. Many factors are well known to be associated with this complication, such as anesthetic drug-induced central nervous system depression, residual effects of muscle relaxants, suboptimal ventilator muscle mechanics as in obesity, impact of surgical incision, increased CO_2 production as in hyperthermia, and pre-existing chronic obstructive pulmonary disease. Anesthesiologists are familiar with these factors, and they are well trained in treating such cases.

Late onset congenital central hypoventilation syndrome is one of the more rare causes of postoperative hypoventilation that may endanger the life of the patient. Herein, we present a case of intractable postoperative hypoventilation in a previously asymptomatic six-year-old child who underwent general anesthesia for multiple dental extractions. The child was diagnosed as having late onset congenital central hypoventilation syndrome. The patient now requires lifelong mechanical ventilator support as a result of his hypoventilation syndrome. The management of the child and the investigations required to confirm the diagnosis are described. Written parental consent was given for publication of this report.

Case report

A six-year-old girl, the product of a consanguineous marriage born full-term through normal spontaneous vaginal delivery, was scheduled for multiple dental extractions under general anesthesia as a daycare patient. During the preoperative evaluation, the parents denied that the child had any history of cardiac or pulmonary disease. There was no history of drug allergy or previous exposure to anesthesia. According to the parents, the child was active and playful at home and had a mild speech delay. She was not gaining weight normally, which was attributed to her dental condition. On examination, the child looked generally well, and apart from poor dentition, the physical examination was unremarkable. Her body weight was 12.5 kg. Routine laboratory investigations, including complete blood count, were within normal limits. The patient's physical status was classified as American Society of Anesthesiologists physical status I. She was premedicated with midazolam 6 mg orally 30 min before surgery.

On arrival in the operating room, the child was awake and communicating actively with her parents and the medical staff. After connecting the patient to the electrocardiogram, pulse oximeter, and noninvasive blood pressure monitor, anesthesia was induced by inhalation of 6% sevoflurane in oxygen and nitrous oxide in a ratio of 1:1. After loss of consciousness, an intravenous cannula was inserted and pediatric saline was started at a rate of 50 $mL \cdot hr^{-1}$. Atracurium 6 mg *iv* and fentanyl 10 μg *iv* were given, and we then proceeded with orotracheal intubation with a size 5 uncuffed endotracheal tube. A throat pack was inserted and mechanical ventilation was started at a tidal volume of 130 mL and a respiratory rate of 20 $breaths \cdot min^{-1}$. Anesthesia was maintained with 0.8 % sevoflurane in oxygen and nitrous oxide in a ratio of 1:2. Dexamethasone 4 mg and metoclopramide 5 mg were administered intravenously while a paracetamol 250 mg suppository was given for postoperative pain relief. The surgical procedure lasted 20 min, and the residual neuromuscular block was reversed with neostigmine 0.6 mg iv and atropine 0.3 mg *iv*. The throat pack was removed, and after oral suctioning, the trachea was extubated because the patient was responding to both painful and verbal stimuli. The patient was then transferred to the postanesthesia care unit. According to the modified Aldrete recovery score,[1] the patient would meet eligibility criteria to be transferred to the ward within 20 min, just after 20 min from the time of tracheal extubation.

Just prior to the anticipated transfer, the child's oxygen saturation fell suddenly. Also, it was observed that she had stopped communicating with the medical staff, and her breathing was no longer adequate. By this point in time, the child had become responsive to painful stimuli only, and while she remained awake, oxygen saturation became normal with oxygen 4 $L \cdot min^{-1}$ by mask. Based on the observed hypoventilation, the child was not maintaining saturation during sleep, a condition thought initially to be an opioid-related side effect. Two doses of naloxone 10 $\mu g \cdot kg^{-1}$ *iv* were administered at five-minute intervals with no response. A second neostigmine 0.5 mg *iv* and atropine 0.3 mg *iv* was given with no effect. The patient's respiratory efforts became greatly reduced with no response to painful stimuli, such that endotracheal intubation could proceed without sedative medications. Manual ventilation commenced afterward. Flumazenil 10 $\mu g \cdot kg^{-1}$ *iv* was then given to exclude a late onset respiratory depressant effect of benzodiazepines. The patient became fully awake and breathing normally after

receiving flumazenil, and she managed tracheal extubation on her own while maintaining normal oxygen saturation. However, after 20 min, the child became drowsy with hypoventilation once again. She was given another dose of flumazenil 10 $\mu g \cdot kg^{-1}$, once more with good response. Due to repeated hypoventilation events which were responsive to flumazenil, the patient was transferred to the intensive care unit (ICU) for observation and for continued maintenance on a flumazenil infusion of 10 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. In the ICU, the child was fully awake and communicating with her mother and medical staff. Two hours later, oral fluids were started while the child maintained oxygen saturation > 93% on room air. However, 12 hr from the start of surgery, another hypoventilation episode occurred during which the child did not respond to either verbal or painful stimuli. Manual ventilation was started with face mask and an Ambu bag connected to oxygen. During the preparation for tracheal re-intubation, the child awoke once again and was able to maintain normal oxygen saturation. At this stage, cardiac or pulmonary abnormalities were excluded on clinical grounds. The parents denied that the child had experienced any prior episodes of easy exhaustion, ptosis, diplopia, or sleep disturbances. There was no family history of neurological or neuromuscular disease. Laboratory investigations of thyroid, liver, and renal function were normal, as were arterial blood gases, creatine kinase, echocardiogram, and chest *x-ray*. The pediatric consultant opined that deterioration of sensorium was correlated with the episode of hypoventilation and recommended to start mechanical ventilation if the episodes of hypoventilation recurred. Within two hours, progressive deterioration in sensorium occurred with hypoventilation, and SpO_2 decreased to 75% while on oxygen. The flumazenil infusion was discontinued as the patient was no longer responding to it. Arterial blood gas results at this time showed pH = 7.1, $PaCO_2$ = 133 mmHg, PaO_2 = 237 mmHg, and base excess = 5.4 $mmol \cdot L^{-1}$. The patient's trachea was intubated, and she was placed on mechanical ventilation in a synchronized intermittent mandatory ventilation (SIMV) mode with a tidal volume of 130 mL and a respiratory rate of 20 $breaths \cdot min^{-1}$. Varying doses of sedative hypnotic drugs, including midazolam 1-5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and fentanyl 1-4 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, were administered to help the child tolerate the endotracheal tube.

At this stage, a diagnosis of familial periodic hypokalemic paralysis was considered, which was associated with hypokalemia during hypoventilation episodes[2]; however, serum K^+ values remained within normal limits during the episodes. The possibility of subclinical neuromuscular disease was considered, but creatine kinase values were within normal limits, and the parents refused muscle biopsy for further diagnosis. To exclude any central pathology, a computed tomography scan, magnetic resonance imaging of the child's head, and an electroencephalogram were undertaken - all related findings were within normal limits. To exclude myasthenia, pyridostigmine was given in a dose of 20 mg qid orally for two days with no response. Fluoroscopy revealed normal diaphragmatic function. Central nervous system stimulants, including caffeine oral drops (90 mg qid for three days) and doxapram (intravenous bolus dose of 3 $mg \cdot kg^{-1}$ over one hour, followed by a continuous infusion of 0.5 $mg \cdot kg^{-1} \cdot hr^{-1}$ for one day), were tried with no response. For the next ten days after exposure to anesthesia, all trials of ventilatory weaning failed due to repeated episodes of hypoventilation associated with sleep. Hence, a tracheostomy was performed, and it was decided to mechanically ventilate the patient's lungs in a SIMV mode during sleep, whether during the day or at night, with a rate of 20 $breaths \cdot min^{-1}$, a preset peak inspiratory pressure of 15 cm H_2O, positive end-expiratory pressure of 5 cm H_2O, and 10 cm H_2O pressure support.

A pediatric neurologist was consulted, and he advised a genetic study for the gene, PHOX2B, to rule out congenital central hypoventilation syndrome. The results of the genetic study confirmed the diagnosis by revealing an expansion mutation in the tested gene. The patient was found to have 25-polyalanine repeat expansion mutation instead of the normal 20-alanine repeat sequence. The child's family (parents and a brother) were advised to seek genetic counselling, and they were referred to the genetic clinic for follow-up. After 65 days in the ICU, it was decided to discharge the patient with a portable ventilator for ventilatory support during sleep and to arrange regular follow-up in the hospital. For one week before the patient was discharged, her parents were trained about tracheostomy care and how to provide home mechanical ventilation. The parents were given a hotline number to contact the hospital in case of emergency.

Discussion

Congenital central hypoventilation syndrome, or Ondine's curse, was reported initially by Mellins *et al*. in 1970.[3] It is a rare lifelong multisystem disorder which commonly occurs during the neonatal period or early infancy. It is characterized by lack of adequate autonomic control of respiration with decreased sensitivity to hypercapnea and hypoxia in the absence of neuromuscular or lung disease or an identifiable brainstem lesion.[4] Since these patients have absent or negligible ventilatory sensitivity to hypercarbia and variable ventilatory sensitivity to hypoxemia during sleep, they are at risk of dying without ventilation during sleep.[4] When awake, these patients lack a perception of dyspnea but maintain conscious control of breathing. The estimated prevalence of the disorder is one case per 200,000 live births.[5] Nearly 1,000 children worldwide have

been confirmed to have congenital central hypoventilation syndrome. However, in the opinion of some, this number is likely underestimated.[6] The disease-causing gene for the congenital central hypoventilation syndrome is the paired-like homeobox gene PHOX2B. Therefore, detecting a mutation in the PHOX2B gene is required to diagnose congenital central hypoventilation syndrome.

The PHOX2B gene is located on chromosome 4p12. The specific mutation appears to be a polyalanine repeat expansion in the second polyalanine repeat sequence in exon 3 of PHOX2B. It is an autosomal dominant disorder with incomplete penetrance.[6] A form of late onset central hypoventilation syndrome (LO-CHS) has been described in at least 11 cases in the literature.[7] Late onset central hypoventilation syndrome presents beyond the neonatal period and as late as during adulthood (three months to 55 yr). Respiratory infection, sedation, or anesthesia apparently triggers the need for permanent nocturnal ventilator support.[8,9] Late onset central hypoventilation syndrome reflects the variable penetrance of the mildest PHOX2B mutations which may require an environmental cofactor to become symptomatic.[6]

Hirschsprung's disease was found in about 20% of patients with CCHS. Individuals with the 20/27 genotype and greater polyalanine expansions are at greatest risk for Hirschsprung's disease. Virtually all individuals with non-polyalanine repeat expansion mutations have Hirschsprung's disease.[10] A 50-70% range of ocular pathologies, including abnormal pupils, abnormal iridis, and strabismus, were found in congenital central hypoventilation syndrome.[11] Therefore, the possibility of this syndrome should be taken into consideration in patients scheduled for surgical repair of Hirschsprung's disease, strabismus surgery, or eye examinations for children under anesthesia,

The child in this case was asymptomatic until she was exposed to general anesthesia. In the immediate postoperative period, we tried to exclude any abnormal response or any residual effect of different anesthetic drugs that had been administered. The initial but temporary response to flumazenil could be attributed to its central analeptic effect.[12] A number of investigations were undertaken to exclude any primary cardiac, pulmonary, hepatic, renal, or central nervous system pathology, diaphragmatic dysfunction or neuromuscular disease. The patient did not respond to central nervous system stimulants, and due to repeated failure of tracheal extubation, a tracheostomy was required. Polysomnography was not done in this case; hence, we cannot comment on respiratory and gas exchange abnormalities during different awake-asleep cycles. However, it was observed that the child was able to comfortably tolerate a $PaCO_2$ of 112 mmHg without overt respiratory distress. Mechanical ventilation in a SIMV mode was instituted during sleep, whether at day or night. The PHOX2B mutation confirmed the diagnosis of LO-CHS. The reason for this congenital syndrome becoming apparent only after exposure to general anesthesia is unknown, but it could be explained, at least in part, by variable penetrance and the degree of mutation of the causative gene.[13]

Clinically, care should be taken to distinguish LO-CHS from a disorder known as rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD). However, children with ROHHAD present with rapid weight gain (15-20 pounds) from three to ten years of age, and they do not have mutations in PHOX2B.[14]

Treatment of LO-CHS will depend on the severity of hypoventilation episodes and the frequency of their occurrence. Most of these patients respond well to sleep ventilation, while others are in need of 24-hr ventilation. There are several reports of success with diaphragmatic pacing with favourable outcomes in some patients.[15,16] Diaphragmatic pacing was not tried in this patient, but it may be considered at a later stage depending on further patient follow-up and the level of care required by the child at home.

In conclusion, this case serves as a reminder to anesthesiologists that congenital central hypoventilation syndrome is a rare lifelong multisystem disorder which may present during the neonatal period as a result of severe genetic mutation in the PHOX2B gene. In mild mutations, a triggering factor, such as sedation or anesthesia, may be required for the syndrome to manifest itself. These patients often require lifelong mechanical ventilatory support, particularly during sleep.

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Conflict of interest None declared.

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