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Case Report

J Med Cases • 2013;4(11):710-714

Perioperative Care of a Child With ROHHADNET Syndrome

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Abstract

ROHHAD syndrome is an acronym, coined in 2007, that outlines a syndrome including *r*apid-onset *o*besity, *h*ypothalamic dysfunction, *h*ypoventilation, and *a*utonomic *d*ysregulation. Common signs and symptoms include obesity, electrolyte imbalance, hypoxemia, thermal dysregulation, and gastrointestinal dysmotility. The high prevalence of neural crest tumors has led to a modification of the acronym to ROHHAD-NET when a neural crest tumor is present. Many of the findings have implications for anesthetic management. We present a 6-year-old girl with ROHHAD syndrome who presented for direct laryngoscopy, bronchoscopy, and adenotonsillectomy. Previous reports of anesthetic care for these patients are reviewed, the end-organ involvement discussed, and options for anesthetic care presented.

Keywords: ROHHAD syndrome; OSA; Central hypoventilation; Autonomic dysregulation; Obesity

Introduction

In 1965, Dr. Fishman was the first to describe a constellation of symptoms which he termed Late Onset Central Hypoventilation Syndrome with Hypothalamic Dysfunction (LO-CHS/HD). In 2007, Dr. Diego Ize-Ludlow renamed the disease using the acronym ROHHAD, a more inclusive term that communicates the major symptoms of the disease including rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation [1, 2]. The most common presenting symptom of ROHHAD syndrome is hyperphagia and obesity secondary to hypothalamic dysfunction. The typical age of onset is between 2 and 4 years. Hypothalamic dysfunction can also result in pituitary dysfunction resulting in electrolyte disturbances (hypernatremia), hyperprolactinemia, hypothyroidism, and growth hormone deficiency. Respiratory signs and symptoms may include obstructive sleep apnea and central hypoventilation, which may result in hypoxemia, hypercarbia, cyanosis, or even cardiorespiratory arrest with sudden death. Autonomic dysregulation may manifest as pupillary dysfunction, strabismus, constipation, diarrhea, hyperthermia, hypothermia, and neural crest tumors. Other symptoms may include generalized tonic-clonic seizures as well as behavioral and developmental abnormalities [1]. The high prevalence of neural crest tumors has led to a modification of the acronym to ROHHAD-NET when a neural crest tumor is present. Given the significant end-organ dysfunction associated with the disorder including obstructive sleep apnea (OSA) and neural crest tumors, surgical intervention and anesthetic care may be required. We present a 6-year-old girl with ROHHAD syndrome who presented for direct laryngoscopy, bronchoscopy, and adenotonsillectomy. Previous reports of anesthetic care for these patients are reviewed, the end-organ involvement discussed, and options for anesthetic care presented.

Case Report

Institutional Review Board approval is not required at Nationwide Children's Hospital (Columbus, Ohio) for the presentation of single case reports. The patient was a 6-year-old, 60.9-kg girl (> 99th percentile for age, 50th percentile for a 20-year-old) with ROHHAD syndrome. She had many of the classic signs and symptoms of ROHHAD syndrome including obesity as well as hypothalamic, respiratory, and

Manuscript accepted for publication August 6, 2013

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doi: http://dx.doi.org/10.4021/jmc1445w

autonomic dysfunction. Hypothalamic dysfunction manifested as rapid weight gain (body mass index of 38.4 kg/M^2), seizures as a result of hypernatremia and diabetes insipidus, hyperprolactinemia, increased thyroid stimulating hormone, and adrenal insufficiency. Respiratory manifestations included chronic hypoxemia and OSA with tonsillar hypertrophy. Autonomic dysregulation included ophthalmological symptoms (myopia and right extropia) and gastrointestinal dysmotility (constipation and gastroesophageal reflux). Additional issues included behavioral problems including depression and anxiety. Past surgical history was significant for dental extractions. Her home medication included desmopressin (0.3 mg PO twice a day), hydrocortisone (5 mg by mouth three times a day), and polyethylene glycol oral powder (Miralax®)(17 g by mouth once a day). The patient was scheduled for adenotonsillectomy to treat OSA, but preoperative testing revealed crackles in right lung base and hypoxemia (oxygen saturation of 90% on room air) due to an antecedent upper respiratory tract infection (URI). The adenotonsillectomy was canceled and performed after the URI resolved, two weeks later. The patient was held *nil per os* for 8 hr prior to the procedure. Pre-operative vital signs revealed an oxygen saturation of 98%, blood pressure of 137/87 mm Hg, and heart rate of 111 beats/minute. Physical examination revealed an obese 6-year-old girl with a Mallampati grade III view of the airway. The patient was transported to the operating room and standard American Society of Anesthesiologists' monitors were placed. Inhalational induction was performed with increasing concentrations of sevoflurane in 100% oxygen. Following anesthetic induction, a 22-gauge peripheral intravenous cannula was placed followed by the administration of dexmedetomidine (20 µg) and midazolam (2 mg). Direct laryngoscopy was performed while maintaining spontaneous ventilation with the insufflation of sevoflurane via the laryngoscope and subsequently the rigid bronchoscope. No significant abnormalities were observed. The trachea was intubated with a 5.5-mm cuffed endotracheal tube (ETT) following completion of the bronchoscopy. With the cuff deflated, an air leak was noted around the ETT at 10 cm H_2O. Breath sounds were equal and bilateral with positive end-tidal carbon dioxide recorded by capnography. Anesthesia was maintained with sevoflurane (expired concentration 1.7-2%) in a combination of air and oxygen to maintain the mean arterial pressure (MAP) within 25% of pre-operative values. Fentanyl (50 µg) and acetaminophen (700 mg) were administered intravenously for postoperative analgesia. Additional medications included dexamethasone (20 mg) and ondansetron (4 mg). Estimated blood loss was minimal. Total intraoperative fluids were 500 mL. Following the surgical procedure, the patient was transferred to the post-anesthesia care unit. During emergence, the patient began to cough and have intermittent breath sounds with a decrease of the oxygen saturation to a low of 77%. Positive pressure ventilation was administered via the ETT tube. The oxygen saturation returned to 99% after cessation of coughing. The patient's trachea was extubated when she was awake. Postoperatively, she was admitted to the Pediatric ICU receiving supplemental oxygen at 3 L/minute via a nasal cannula to maintain an oxygen saturation ≥ 93%. The oxygen was slowly weaned over the ensuing 8 hr. Postoperative analgesia was provided by intermittent doses of fentanyl and around the clock acetaminophen. The remainder of her postoperative course was uncomplicated and she was discharged home on postoperative day 2.

Discussion

ROHHAD syndrome shares many clinical similarities with congenital central alveolar hypoventilation syndrome or Ondine's curse. Although the latter was once believed to only occur in newborns, Antic et al have demonstrated that a mild variant may not have clinically significant manifestations until later in childhood or even the adult years [3]. A genetic mutation in the paired-like homeobox 2b gene is responsible for Ondine's curse (congenital central alveolar hypoventilation syndrome) [4]. This genetic mutation is not present in patients with ROHHAD, establishing a means by which the two clinically similar syndromes may be differentiated. A notable feature of ROHHAD syndrome is the apparently normal development during the first 2 - 4 years of life followed by the sudden onset of hypothalamic dysfunction manifested as the onset of rapid weight gain and obesity. This weight gain is dramatic, with some patients gaining as much as 40 pounds over 4 months. Other hypothalamic abnormalities may be detected in the months following the rapid onset of obesity. Despite increased recognition of the disorder, its incidence is rare with fewer than 100 reported cases in the literature. No specific cause has been identified to explain the disorder. Given the multi-system involvement that may be seen with ROHHAD syndrome, perioperative care during surgical procedures can be challenging [5, 6].

Of primary concern to the anesthesia provider are potential problems with airway management during anesthetic induction and endotracheal intubation. One such challenge is difficulty with endotracheal intubation due to obesity and upper airway obstruction. In the adult population, it has been demonstrated that sleep apnea syndromes including OSA are independent risk factors for difficult endotracheal intubation [7, 8]. In many patients, this relates not only to the weight or body mass index, but also correlates with the neck circumference. In a study of 123 obese adults, Kim et al noted that difficult laryngoscopy correlated with the ratio of the neck circumference to the thyromental distance (NC/TM) [9]. Of the various relationships that they investigated, the NC/TM ratio had the highest sensitivity, a negative predictive value, and the largest area under the curve on a receiver operator curve. When providing anesthetic care for a patient

with ROHHAD syndrome, the anesthetic provider should be prepared for the possibility of a difficult airway. The necessary equipment including tools for fiberoptic intubation and indirect laryngoscopy should be readily available [10, 11]. In general, spontaneous ventilation should be maintained until the ability to bag-valve-mask ventilation is demonstrated. Given these concerns, we chose to maintain spontaneous ventilation with an inhalation induction using sevoflurane in 100% oxygen. Direct laryngoscopy was performed while maintaining spontaneous ventilation with the insufflation of sevoflurane via the laryngoscope followed by endotracheal intubation.

OSA and upper airway concerns may also impact premedication and anesthetic induction. If premedication is administered, the patient should be monitored appropriately to detect respiratory insufficiency prior to transport to the operating room. Even the usual premedicant doses of oral midazolam (0.3 - 0.5 mg/kg) can impact respiratory function in these patients. During the induction of anesthesia, inhibition of the normal dilator musculature of the oropharynx and relaxation of the genioglossus muscle may result in upper airway obstruction. Placement of an oral or nasal airway may be necessary to overcome soft-tissue obstruction. Alternatively, a laryngeal mask airway may be used to provide an unobstructed conduit to the glottic opening thereby improving gas exchange and facilitating anesthetic induction [12].

In addition to anticipating difficulty with anesthetic induction and endotracheal intubation, anesthetic providers must also consider the perioperative respiratory complications that may occur in these patients related to alterations in central control of ventilation. These factors combined with the propensity for upper airway obstruction may lead to postoperative respiratory failure. General precautions include appropriate perioperative monitoring, tracheal extubation when the patient is fully awake and the residual effects of the anesthetic agents have dissipated, as well as the use of adjunctive agents for postoperative analgesia to limit the need for perioperative opioids [13]. Given their low blood:gas and blood:fat solubility, the new volatile anesthetic agents (sevoflurane or desflurane) offer the advantage of providing an appropriate depth of anesthesia while allowing for rapid awakening with minimal residual effects. In the neonatal population, these agents have been shown to limit the incidence of postoperative apnea [14, 15]. While opioids may be required for postoperative analgesia following painful surgical procedures, we would recommend ongoing monitoring of the patient's respiratory status in the ICU setting, the use of shorter-acting agents (fentanyl versus morphine), and the use of adjunctive agents to decrease the total dose. Additionally, given the potential for increased sensitivity to the respiratory depressant effects of opioids in patients with OSA and ROHHAD syndrome, we chose to titrate the opioid dose intraoperatively based on the patient's respiratory rate once spontaneous ventilation had resumed [16-18].

Total opioid requirements may be decreased by the use of adjunctive agents including dextromethorphan, ketamine, dexmedetomidine or acetaminophen [19-21]. In our patient, we administered a single intraoperative dose of dexamethasone, which has also been shown to improve the postoperative course and decrease opioid requirements [22]. Acetaminophen was administered intraoperatively followed by fixed interval dosing during the postoperative period. Although, non-steroidal anti-inflammatory agents have also been demonstrated to have an opioid sparing effect, given the potential for increased bleeding, we generally avoid these agents following adenotonsillectomy [23].

Autonomic dysregulation has also been shown to be an associated co-morbid condition of ROHHAD syndrome. This may manifest as alterations in central temperature control, gastrointestinal motility issues, altered perception of pain, syncope, brady and tachy-arrhythmias, and altered control of sweating. The potential impact of such autonomic dysregulation in the etiology of sudden death in patients with ROHHAD syndrome must be considered and further emphasizes the need for postoperative monitoring of respiratory, hemodynamic, and cardiac function in an ICU setting. Potential therapeutic interventions in the treatment of patients with autonomic dysfunction have been nicely reviewed and summarized previously [6, 24]. In our patient, the manifestations of autonomic dysregulation included ophthalmological symptoms (myopia and right extropia) and gastrointestinal dysmotility (constipation and gastroesophageal reflux). Although there may be a concern for the risk of aspiration during anesthetic care in patients with gastroesophageal reflux, the symptomatology was minimal in our patient and controlled with medication. In patients with more significant manifestations, various maneuvers (cricoid pressure, rapid sequence intubation) or medications (metoclorpramide, H2-antagonists) may be indicated to limit the risk for perioperative aspiration [25].

Endocrine dysfunction resulting from ROHHAD syndrome may include diabetes insipidus, adrenal insufficiency, and adrenal tumors. Our patient had a history of seizures due to hypernatremia and diabetes insipidus, hyperprolactinemia, increased thyroid stimulating hormone, and adrenal insufficiency. Although our patient's symptoms related to diabetes insipidus were transient and controlled with DDAVP administration, perioperative recurrences may be seen or treatment required for ongoing problems. Chronic hypernatremia, related to ongoing diabetes insipidus, is common in patients with ROHHAD syndrome. In general, treatment options include preoperative evaluation of serum electrolytes, monitoring of fluid status including urine output, replacement of excessive urinary losses with hypotonic fluids to avoid hypernatremia, and replacement of antidiuretic hormone with either intranasal administration of DDAVP or the intravenous administration of vasopressin [26]. Based on clinical signs and symptoms, adrenal function should be evaluated pre-

operatively. Our patient had previously been diagnosed and was maintained on hydrocortisone supplementation. Given the brevity of the procedure and its limited physiologic impact, stress dosing was not employed. For major procedures, stress dosing of hydrocortisone may be needed [2]. To limit the perioperative effects of these conditions on our patient, her usual morning dose of hydrocortisone and DDAVP were administered. Perioperative signs and symptoms of hypotension, hypoglycemia, and GI manifestations including emesis may be related to adrenal insufficiency [2]. Additionally, given the potential association of neural ectodermal tumors and ROHHAD syndrome, the pre-operative history should include questions regarding the presence of signs and symptoms indicative of catecholamine excess including tachycardia, hypertension, diaphoresis, and headache.

Given the rarity of ROHHAD syndrome, there is only one previous report in the literature discussing its perioperative implications [6]. The report outlined the perioperative care of two patients with ROHHAD syndrome. The first patient was a 4.8-year-old girl who presented with classic symptoms of ROHHAD syndrome including hyperphagia and obesity, hypoventilation, hypernatremia, hyperprolactinemia, constipation, and diaphoresis. She was scheduled for a tracheostomy under general anesthesia so that long term ventilator support could be provided during sleep. Although prior procedures (adrenal ganglioneuroblastoma resection and adrenalectomy) performed under general anesthesia were uneventful, the anesthetic provider was concerned about the airway and respiratory status during anesthetic induction. On arrival in the operating room, a dexmedetomidine infusion was started at 0.2 μg/kg/hr followed by anesthetic induction with ketamine (2 mg/kg) and atropine (15 μg/kg). This was followed by endotracheal intubation. Neuromuscular blockade with rocuronium was provided when movement occurred despite an adequate depth of anesthesia. The procedure was uneventful and the patient was monitored in a pediatric ICU setting before discharge on postoperative day 2.

The second patient was a 9-year-old girl who presented for colonoscopy and colonic manometry catheter placement under general anesthesia. This patient also exhibited hyperphagia and obesity, hypernatremia, hypoventilation, constipation, as well as developmental delay. Sevoflurane was the sole agent used for the induction and maintenance of an uneventful procedure. Endotracheal intubation was performed under inhalational anesthesia with sevoflurane. Again, particular attention was given to monitoring the patient's respiratory status, using end-tidal carbon dioxide monitoring throughout the perioperative period.

ROHHAD syndrome is an uncommon disease that may have multiple organ system involvement as was seen in our patient. Obesity, hypoventilation, thermal dysregulation, and autonomic dysfunction may be especially concerning to the anesthesia provider. Increasing awareness and knowledge regarding this disorder will allow for improved patient care. Establishing the diagnosis of ROHHAD syndrome, allows for optimal perioperative preparation, assessment, and monitoring.

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