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Anesthetic care during posterior spinal fusion in a patient with Prader-Willi syndrome

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Keypoints

1. Prader-Willi Syndrome (PWS) is a neurodevelopmental genomic imprinting disorder affecting chromosome 15.
2. Comorbid respiratory conditions that may impact perioperative care include pre-existing obstructive sleep apnea or sleep disordered breathing, scoliosis with restrictive lung disease, and associated hypotonia.
3. Cardiovascular involvement may include arrhythmias, conduction abnormalities, premature ventricular contractions, and obesity related hypertension. Additionally, there is an increased incidence of congenital heart disease when compared to the general population.
4. Additional end-organ involvement may include the endocrine (adrenal and growth hormone deficiency), gastrointestinal (aspiration risk), and central nervous systems.

Abstract

Prader-Willi syndrome (PWS), originally described in 1956, is a genomic imprinting disorder affecting chromosome 15. Three genetic subtypes have been recognized, the most common of which is the paternal chromosome 15q11-q13 deletion accounting for 65-75% of cases. Patients with PWS manifest several distinguishing characteristics including infantile hypotonia, cognitive dysfunction, hyperphagia leading to obesity, short stature, orthopedic deformities, and hypothalamic dysfunction. Other important clinical manifestations include short stature, developmental delay, sleep disturbances including obstructive sleep apnea, cognitive disabilities, seizures, behavioral problems, and hypothalamic dysfunction. Due to associated end-organ involvement, surgical procedures are often required in PWS patients. We present a 12-year-old adolescent with Prader-Willi syndrome who required anesthetic care during a posterior spinal fusion to treat scoliosis. The potential perioperative implications of these patients are reviewed and options for anesthetic care presented.

Keywords

Prader-Willi syndrome, posterior spinal fusion, scoliosis, anesthesia

Introduction

Prader-Willi Syndrome (PWS) is a neurodevelopmental genomic imprinting disorder affecting chromosome 15 that was originally described in 1956.[1,2] Three genetic subtypes have been identified including the paternal chromosome 15q11-q13 deletion (65-75%), maternal uniparental disomy 15 (20-30%), and an imprinting defect (1-3%).[2] Early findings of PWS include infantile hypotonia and a poor suck which can lead to failure to thrive. With age, hyperphagia develops leading to the potential for severe, life-threatening obesity.[1-3] Other important clinical manifestations of PWS include short

stature, developmental delay, sleep disturbances including obstructive sleep apnea (OSA) or sleep-disordered breathing, cognitive disabilities, seizures, behavioral problems, and hypothalamic dysfunction.[2] The estimated prevalence of this complex genetic disorder is 1 in 10,000-30,000 with an equal gender distribution.[4] Due to associated end-organ involvement, surgical procedures are often required in PWS patients including surgery for scoliosis, orchiopexy, adenotonsillectomy to treat OSA, and ophthalmologic surgery to correct strabismus.[1] These patients have an increased risk of perioperative complications related to hypotonia, obesity, OSA, cardiovascular involvement, metabolic imbalances, and altered expression of gamma-amino butyric acid (GABA) receptors.[1] We present a 12-year-old adolescent with PWS who required anesthetic care during a posterior spinal fusion to treat scoliosis. The potential perioperative implications of these patients are reviewed and options for anesthetic care presented.

Case report

Preparation of this case report followed the guidelines of the Institutional Review of Nationwide Children's Hospital (Columbus, Ohio). A 12-year-old, 56.5-kilogram adolescent male with PWS presented for treatment of syndromic scoliosis. The diagnosis of Prader-Willi syndrome was suspected during the neonatology period due to the presence of hypotonia and was subsequently confirmed by chromosomal analysis. Additional past medical history and comorbid conditions included sleep apnea, gastroesophageal reflux disease, juvenile idiopathic arthritis, Meckel's diverticulum, chronic otitis media, developmental delay, and attention-deficit hyperactivity disorder (ADHD). Past surgical history included circumcision, gastrostomy tube placement, adenotonsillectomy, placement of tympanostomy tubes, orchiopexy, herniorrhaphy, and supra-glottoplasty. There was no history of significant perioperative complications during these procedures. Due to progressive scoliosis, the patient was scheduled for posterior spinal fusion. At the time of surgery, medications included methylphenidate (27 mg by mouth every day), topiramate (150 mg by mouth every day), guanfacine (2 mg by mouth every day), gabapentin (300 mg by mouth every night), sertraline (100 mg by mouth every day), cholecalciferol (5,000 unit oral tablet every morning), polyethylene glycol (17 grams with liquid every day), loratadine (10 mg by mouth every day) and somatropin (1.3 mg inject subcutaneous daily). Physical examination revealed a well appearing, normocephalic adolescent male with a Mallampati class II airway, normal mouth opening, normal dentition and a thyromental distance of more than 3 finger breadths. The cardiorespiratory examination was normal. Preoperative laboratory evaluation including renal function, coagulation function (prothrombin time, international normalized ratio, and partial thromboplastin time), and complete blood count were normal. The patient was held *nil per os* for 8 hours prior to surgery and was transferred to the operating room where routine American Society of Anesthesiologists' monitors were applied. The patient was allowed to breath 70% nitrous oxide in oxygen and an 18 gauge peripheral intravenous cannula was placed. Anesthesia was induced with intravenous propofol (3 mg/kg), lidocaine (1 mg/kg) and sufentanil (0.25 µg/kg). Bag-valve-mask ventilation was provided without difficulty. Neuromuscular blockade was provided by the administration of intravenous rocuronium (0.3 mg/kg). Direct laryngoscopy revealed a Cormack-Lehane grade 1 view and the trachea was intubated with a 6.0 mm cuffed ETT. After anesthetic induction and endotracheal intubation, a second peripheral intravenous cannula and a right radial arterial cannula were placed. Per our usual practice to allow for neurophysiological monitoring during spinal surgery, anesthesia was maintained with desflurane titrated to maintain the bispectral index (BIS) at 50-60 and a sufentanil infusion of 0.3-0.7 µg/kg/hour to maintain the mean arterial pressure at 55-65 mmHg.[5] This was supplemented by the continuous infusion of lidocaine (20 µg/kg/min), ketamine (0.25 mg/kg/hour), and esmolol (5-10 µg/kg/min). Baseline neurophysiological monitoring including motor evoked potentials (MEP) and

somatosensory evoked potentials (SSEP's) were obtained. Tranexamic acid was administered for prevention of fibrinolysis and to limit intraoperative blood loss (50 mg/kg bolus dose followed by an infusion at 5 mg/kg/hour). The patient was turned and positioned prone on the operating room table. Forced air warming and the infusion of warmed intravenous fluids was used to maintain normothermia. The surgical procedure was completed in 7 hours 5 minutes with an estimated blood loss of 900 mL which was washed and returned via the cell saver. Intraoperatively, a phenylephrine infusion (0.2-0.4 µg/kg/min) was required for 2-2.5 hours to maintain the MAP at the desired value during spinal distraction. Intraoperative fluids included 1700 mL of Normosol-R® and 750 mL of 5% albumin. Arterial blood gas analysis and hemoglobin concentrations were measured periodically during the surgical procedure. The postoperative hemoglobin was 9.1 gm/dL on postoperative day 1. No allogeneic blood products were administered during the intraoperative or postoperative course. Acetaminophen (1000 mg) and ketorolac (30 mg) were administered intravenously to supplement postoperative analgesia. Ondansetron (4 mg) and dexamethasone (4 mg) were administered for postoperative nausea and vomiting prophylaxis. At the completion of surgery, the patient was turned supine and sugammadex (120 mg) was administered to reverse residual neuromuscular blockade. The patient's trachea was extubated, and he was transferred to the post-anesthesia care unit (PACU). Postoperative analgesia was provided by hydromorphone delivered by patient-controlled analgesia and the fixed interval administration of ketorolac and acetaminophen. His postoperative course was unremarkable and he was discharged home on postoperative day 6.

Discussion

As with any anesthetic encounter, effective perioperative care begins with a preoperative evaluation including a medication review, identification of the end-organ impact of the primary disease process, review of associated comorbid conditions, and a consideration of the implications of the intended surgical procedure. The multisystem involvement of PWS raises considerations for the anesthetic management of this patient population. Of primary concern are comorbid involvement of the upper airway and respiratory system including pre-existing OSA, scoliosis, and associated hypotonia.[6] As body mass index (BMI) increases, difficulties with bag-valve-mask-ventilation and endotracheal intubation may be more common. No such concerns were identified during the preoperative airway examination of our patient including Mallampati scoring, thyromental distance, and mouth opening. If the preoperative physical examination or past history suggest that airway management may be problematic, the appropriate equipment for dealing with the difficult airway including an indirect video-laryngoscope should be readily available during the induction of anesthesia.[7,8]

As noted in our patient, OSA is frequent in patients with PWS. The severity of OSA does not always correlate with increasing BMI.[9] The incidence of OSA has been estimated to be as high as 80% and is often present in association with adenotonsillar hypertrophy, obesity, craniofacial abnormalities, and neuromuscular weakness.[1,9-11] Like our patient, many PWS patients may have a history of previous adenotonsillectomy to treat OSA. However, residual OSA may still be present even after adenotonsillectomy. As OSA increases the risk of respiratory complications during anesthesia, preoperative identification of the severity of symptoms is essential. While the time-honored method for identifying and quantifying the severity of OSA is polysomnography, the preoperative history and physical examination with brief screening tools may be equally effective and a more time and cost-efficient means of identifying OSA.[12] Perioperative concerns in patients with OSA and sleep disordered breathing include an increased incidence of perioperative airway adverse events including laryngospasm, respiratory insufficiency with oxygen desaturation, and an increased sensitivity to opioid analgesia.[13] In addition to OSA and associated skeletal muscle hypotonia (see below),

scoliosis may significantly impact perioperative respiratory function. As the degree of curvature progresses, restrictive lung disease may progress with a decrease in respiratory compliance.[14] As the Cobb angle increases to greater than 65º, lung volumes are reduced, and ventilation/perfusion mismatch can develop. In severe scoliosis with a Cobb angle >100°, pulmonary hypertension may develop.[15] Scoliosis surgery produces an immediate and transient decrease in vital capacity of up to 40% in virtually all patients even those with idiopathic scoliosis without co-morbid conditions.[16] Patients who have abnormal results on their pulmonary function test, particularly a forced vital capacity of less than 30%, or those who have hypercapnia preoperatively have been shown to have a higher need for postoperative ventilation.[15,16] Preoperative preparation should include the aggressive treatment of respiratory infections and as cognitive function permits, instruction regarding the use of techniques such as incentive spirometry with the consideration of the use of non-invasive ventilation techniques following tracheal extubation.[17,18] Residual effects of anesthetic agents and neuromuscular blocking medications may impact upper airway control and postoperative respiratory function. Intraoperatively, the use of short acting agents (desflurane and short acting synthetic opioids infusions such as remifentanil, fentanyl or sufentanil) may speed recovery from anesthesia and lessen the impact of these agents on postoperative respiratory function and upper airway control. When ongoing opioid administration is required postoperatively, continuous monitoring of respiratory function is suggested.

Although no comorbid cardiovascular involvement was noted in our patient, patients with PWS may have associated arrhythmias, conduction abnormalities, premature ventricular contractions, and hypertension.[6] Cardiovascular involvement results not only from PWS-associated obesity and OSA, but also other associated features including growth hormone (GH) deficiency as well as chromosomal 15 deletions of Nuclear Receptor Subfamily 2 Group F Member 2 (NR2F2) and cardiac alpha actin (ACTC) genes.[19] GH deficiency may cause PWS patients to have smaller left ventricles and lower systolic function increasing the risk of myocardial dysfunction.[2] The NR2F2 and ACTC genes are involved with cardiac development and their deletion may increase the incidence of congenital heart disease.[19,20] More recently, the incidence of congenital heart disease has been shown to be 5.4-18.7 times higher than the general population.[21] Due to the increased risk of these cardiovascular abnormalities, a preoperative electrocardiogram and echocardiograph may be indicated based on the patient's clinical history. Additionally, blood pressure assessment during the pre-anesthesia evaluation is recommended.

Central nervous system involvement includes hypotonia, seizures, intellectual impairment, and altered expression of gamma-amino butyric acid (GABA) receptors. The safety of the use of succinylcholine should be considered in any patient with involvement of skeletal muscle (hypotonia), motor nerves or the neuromuscular junction.[22] Mayhew and Taylor reported a malignant hyperthermia-like picture with the rapid increase in body temperature following the administration of succinylcholine during halothane anesthesia in one of their patients.[23] However, the postoperative creatinine phosphokinase level was not elevated and no other manifestations of MH were noted. Additionally, other authors have reported the safe use of succinylcholine in patients with PWS.[19,20] Given the associated hypotonia, there may be perioperative concerns regarding the response to non-depolarizing neuromuscular blocking agents (NMBAs) with the potential for prolonged blockade even following intermediate-acting agents.[24] However, anecdotal reports have demonstrated the safe use of various non-depolarizing NMBAs including pancuronium, atracurium, vecuronium, and rocuronium without evidence of prolonged effects. In our patient, given that the surgical procedure included neurophysiological monitoring (MEPs and SSEPs), we used a small dose of rocuronium (0.3 mg/kg) for endotracheal intubation. Its effects had dissipated by the time surgical positioning had been accomplished and the first set of

neurophysiological monitoring obtained. Furthermore, the novel reversal agent, sugammadex, offers the potential for rapidly and effectively reversing neuromuscular blockade, even in the setting of associated neuromuscular disease.[25] Anecdotal experience and our current report supports the successful use of sugammadex to reverse residual neuromuscular blockade in patients with PWS.[26,27]

Most patients with PWS have developmental delay and mental retardation with an intelligent quotient (IQ) in the 60-80 range. This may lead to problems with communication and patient cooperation during the perioperative period. Anecdotal reports have noted the potential for aggressive behavior toward medical personnel. The prevalence of seizures in patients with PWS is approximately 16%, being most common with the deletion genotype.[28] Simple maneuvers to limit the potential for perioperative seizures include a documentation of therapeutic anticonvulsant levels prior to the surgical procedure and continuation of therapy during the perioperative period including the administration of routine anticonvulsant medications the day of the procedure.[29] When enteral administration is not feasible, alternative routes of delivery or alterative agents should be used. Consultation with the neurology or pharmacology service is suggested when questions arise concerning dosing conversion from enteral to intravenous administration or for the choice of substitute anticonvulsant medications.

There are three gamma aminobutyric acid (GABA) receptor subunit genes in the 15q11-q13 region, which are deleted in the majority of PWS patients.[2] GABA is an important inhibitory neurotransmitter and the altered expression of these genes may play a role in appetite, visual perception, and memory.[2] Additionally, it has been postulated that the altered expression of these genes may change the response to anesthetic agents including propofol and the benzodiazepines leading to prolonged recovery times.[1] However, the exact clinical implications of these findings requires further study.[30,31] Endocrine involvement may include adrenal insufficiency (CAI), obesity related diabetes mellitus (DM), and GH deficiency (see above). CAI may have a prevalence as high as 60% in the PWS population, but often goes undiagnosed as baseline cortisol levels are normal.[32] The authors concluded that the high percentage of CAI in PWS patients might explain the high rate of sudden death, particularly during infection-related stress. They go on to recommend consideration of treatment with hydrocortisone during acute illness in PWS patients unless CAI has recently been ruled out. Anecdotal reports describe the need for glucocorticoid therapy intraoperatively to manage hypotension.[33] The implications of these findings during the perioperative period remain uncertain. Although routine preoperative testing with an ACTH stimulation test may not be indicated in all patients, early institution of hydrocortisone therapy is suggested for the treatment of hypotension or perioperative cardiovascular concerns. PWS patients have a 10-fold increased incidence of obesity and a 9-fold increased incidence of developing metabolic syndromes such as type 2 DM.[34]

Other miscellaneous concerns include gastrointestinal (GI) involvement with rumination, disorders of temperature regulation, and difficult peripheral venous access. GI involvement may include lowered esophageal sphincter tone, decreased GI motility, and rumination syndromes. These conditions may increase the risk of perioperative aspiration.[35] Hypothalamic dysfunction may alter intraoperative temperature regulation with reports of both hypothermia and hyperthermia thereby mandating continuous temperature monitoring. Obesity may impact perioperative positioning and increase the difficulty of placement of venous and arterial vascular catheters.[36]

PWS is a complex genetic disorder resulting from a deletion on chromosome 15. Comorbid involvement may include several organ systems including the airway, respiratory, cardiovascular, endocrine, gastrointestinal, and central nervous systems. Additional issues are presented by the frequent association of obesity. These multi-organ involvement poses several concerns during the perioperative period (Table 1). Even with appropriate preparation and perioperative care, perioperative mortality and

morbidity may occur. The preoperative assessment of end-organ impairment by the primary disease process, consideration of the implications of the proposed surgical procedure, and perioperative preparation can improve the perioperative care of these patients.

Table 1: Perioperative considerations of Prader-Willi syndrome

1. Airway and respiratory involvement
    a. Obesity and airway related issues including difficulties with bag-valve-mask ventilation or endotracheal intubation
    b. Obstructive sleep apnea and sleep disordered breathing
    c. Upper airway effects of hypotonia
    d. Repeated upper respiratory infections
2. Respiratory concerns
    a. Restrictive lung disease from scoliosis
    b. Skeletal muscle hypotonia with poor cough effort and impaired clearance of secretions
3. Hemodynamic and cardiovascular concerns
    a. Congenital heart disease
    b. Arrhythmias and conduction abnormalities
    c. Premature ventricular contractions
    d. Obesity related hypertension
4. Central nervous involvement
    a. Hypotonia
    b. Impaired upper airway control and cough effort
    c. Altered expression of gamma-amino butyric acid (GABA) receptors
    d. Developmental delay
    e. Seizures
5. Endocrine involvement
    a. Central adrenal insufficiency
    b. Obesity
    c. GH hormone deficiency
    d. Diabetes mellitus
6. Gastrointestinal involvement
    a. Gastrointestinal reflux
    b. Rumination syndromes
7. Miscellaneous
    a. Difficult peripheral vascular access
    b. Obesity-related intraoperative positioning
    c. Impaired temperature control

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