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Perioperative care of a child with Sanfilippo syndrome for adenotonsillectomy

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Keypoints

1. Sanfilippo syndrome (MPS III), is an autosomal recessive, lysosomal storage disease that results from a congenital deficiency of one of the four enzymes involved in the catabolism of glycosaminoglycan (GAG) heparin sulfate.
2. Like all of the MPS, intracellular accumulation of the GAGs results in cellular and physiologic dysfunction in various organ systems including airway infiltration, cardiac and respiratory involvement, cognitive retardation, hepatosplenomegaly, and skeletal deformities including kyphoscoliosis.
3. Although less common than with other forms of MPS, upper airway obstruction and difficulties with endotracheal intubation may be encountered.
4. Given the potential for cardiac involvement, particularly left side valvular insufficiency or stenosis, preoperative echocardiography is recommended.

Abstract

The mucopolysaccharidoses (MPS) are a group of inherited conditions with lysosomal enzymatic deficiencies resulting in the inability to metabolize glycosaminoglycans. The MPS are separated into 7 major types, based on the underlying enzymatic defect. MPS type III or Sanfilippo syndrome is an autosomal recessive disorder, resulting from the congenital deficiency of one of the four enzymes involved in the catabolism of glycosaminoglycan heparin sulfate. Given the multi-system involvement including the airway, respiratory, cardiovascular, and central nervous systems, patients with MPS are at increased risk during anesthetic care or procedural sedation related to airway obstruction, excessive airway secretions, skeletal restriction of cervical spine movement, infiltration of airway structures, neurologic impairment, and frequent respiratory infections. We present a 5-year-old child with MPS type III (Sanfilippo syndrome) who required anesthetic care during adenotonsillectomy. The perioperative implications of Sanfilippo syndrome are presented, previous reports of anesthetic care reviewed, and options for anesthetic care discussed.

Keywords

mucopolysaccharidosis type III, Sanfilippo syndrome, pediatric anesthesia

Introduction

The mucopolysaccharidoses (MPS) are a group of inherited conditions with lysosomal enzymatic deficiencies resulting in the inability to metabolize mucopolysaccharides or glycosaminoglycans (GAGs).[1] The first recognition of the clinical manifestations of a MPS (Hunter disease or MPS type II) was reported by Dr. Charles Hunter in 1917.[2] The GAGs are long unbranched chains of sugar molecules that contain a repeating disaccharide

unit. These compounds are found throughout the body in all connective tissues, the extracellular matrix, and on the surfaces of many cell types, functioning in cell adhesion and cellular signaling.[3] Inadequate degradation of GAGs and their accumulation in lysosomes and other intracellular structures leads to secondary adverse effects on cellular function including autophagy, apoptosis, and mitochondrial dysfunction. The multi-system dependence on the GAGs for normal cellular function results in severe clinical signs and symptoms including coarse facial features, airway infiltration, cardiac and respiratory involvement, cognitive retardation, hepatosplenomegaly, skeletal deformities including kyphoscoliosis, corneal clouding.[4]

The MPS are divided into 7 major types, based primarily on the underlying enzymatic defect.[4] The varied enzymatic defect results in varied clinical phenotypes, biochemical alterations, age at presentation, life span, and clinical involvement. Type II MPS is inherited as an X-linked trait while the others are dependent on autosomal recessive inheritance. Given the multi-system involvement including the airway, respiratory, cardiovascular, and central nervous systems, MPS patients are at increased risk during anesthetic care or procedural sedation related to airway obstruction, excessive airway secretions, skeletal restriction of cervical spine movement, infiltration of airway structures, neurologic impairment, and frequent respiratory infections. We present a 5-year-old child with MPS type III (Sanfilippo Syndrome) who required anesthetic care during adenotonsillectomy. The perioperative implications of San Filippo syndrome are presented, previous reports of anesthetic care reviewed, and options for anesthetic care discussed.

Case report

Review of this case and presentation in this format was in accordance with the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). A 24.6-kg, 5-year-old boy with Sanfilippo syndrome (MPS type-IIIB, α-N-acetyl-glucosaminidase deficiency) presented for adenotonsillectomy and bilateral inferior turbinate reduction due to tonsillar hypertrophy, snoring, sleep-disordered breathing, inferior turbinate hypertrophy, and chronic nasal congestion. Associated comorbid conditions included autism spectrum disorder with accompanying language impairment and intellectual disability and mixed conductive and sensorineural hearing loss in the left ear. The diagnosis of MPS type III was made at 4 ½ years of age when he was referred to the genetics clinic for evaluation of dysmorphic features and behavioral issues. Diagnosis was confirmed by urinary GAGs and white blood cell enzyme testing for MPS III. Previous anesthetic care for magnetic resonance imaging (MRI) was unremarkable. Current medications included clonidine (0.1 mg by mouth at bedtime), iron supplementation (45 mg by mouth once a day), prednisolone (20 mg by mouth once a day), cholecalciferol (3,000 units by mouth once a day), and montelukast sodium (4 mg by mouth once a day). Physical examination revealed coarse facial features consistent with the diagnosis of MPS type III. Airway examination revealed large tonsils with a Mallampati score of III. Cardiac and respiratory examinations were unremarkable. Preoperative echocardiogram was negative. The patient was held nil per os for 6 hours. Premedication included oral midazolam (0.5 mg/kg). The difficult airway cart was brought into the operating room as well as the indirect laryngoscope (Glidescope®). The patient was transported to the operating room and routine American Society of Anesthesiologists' monitors were placed, followed by the inhalation induction of anesthesia with sevoflurane in nitrous oxide and oxygen. Peripheral intravenous access was achieved on the second attempt and propofol (3 mg/kg) was administered intravenously. Manual in-line stabilization of the cervical spine was provided. Direct laryngoscopy was performed with a 1.5 Wis-Hipple blade which revealed a Cormack-Lehane grade II-III view. Indirect laryngoscopy was performed with the Glidescope® which provided a grade I view. A 5.0 mm cuffed endotracheal tube was placed. The cuff was inflated to seal the airway to CPAP 20 cmH2O. Anesthesia was maintained with

sevoflurane (expired concentration 2-4%) in air and oxygen. Analgesia was provided by morphine (2 mg). Prophylaxis against postoperative nausea and vomiting included ondansetron (4 mg) and dexamethasone (4 mg). Additional medications included dexmedetomidine (0.3 µg/kg). The surgical procedure lasted approximately 35-40 minutes and was completed without complications. Intraoperative fluids included lactated Ringer's (300 mL). At the completion of the surgical procedure, the patient's trachea was extubated when he was awake and he was transported to the post-anesthesia (PACU). A single dose of fentanyl (12.5 µg) was administered in the PACU to provide additional analgesia. The patient was admitted to the inpatient ward and monitored with continuous pulse oximetry overnight. The patient's postoperative course was unremarkable and he was discharged home the next day.

Discussion

MPS type III, also known as Sanfilippo syndrome is an autosomal recessive, lysosomal storage disease with a prevalence of 0.28-4.1 per 100,000 live births.[5,6] MPS III results from a congenital deficiency of one of the four enzymes involved in the catabolism of glycosaminoglycan heparin sulfate. Based on the specific enzymatic deficiency, MPS III is divided into 4 subtypes (Type A-D), which share similar phenotypic expression and clinical features. Deficiency of any of these enzymes manifests as a neurodegenerative disorder with progressive worsening behavioral disturbances with rapidly declining motor and cognitive function. MPS patients are at increased risk during anesthetic care or procedural sedation related to airway obstruction, excessive airway secretions, skeletal restriction of cervical spine movement, infiltration of airway structures, neurologic impairment, and frequent respiratory infections.

Anesthetic care begins with a thorough preoperative history and physical examination with identification of the end-organ involvement. Although the somatic features in MPS III may be milder when compared with Hurler and Hunter disease (MPS I and MPS II), airway involvement with MPS III may include excessive secretions, macroglossia, involvement of the cervical spine, and abnormal airway anatomy which may lead to upper airway obstruction during anesthetic induction or procedural sedation.[7] Significant anatomical changes of the vocal cords and trachea have been reported in pediatric patients with MPS using computed tomography imaging.[8] In addition to the changes of the shape of the vocal cords and trachea, the tracheal surface area has been reported to be smaller. Upper airway obstruction may occur during sleep, sedation or the induction of anesthesia as a result of thickened pharyngeal and laryngeal structures including the tonsils and adenoids, narrowed nasal passages, and copious airway secretions. Lower airway obstruction can result from malformed tracheal cartilage, redundant respiratory epithelium, airway edema due to recurrent infections or reactive airway disease. Airway involvement may result in difficulties during endotracheal intubation. Given these concerns, the appropriate equipment for dealing with the difficult airway including indirect video-laryngoscopy should be readily available prior to anesthetic induction.[9] General anesthesia can be induced by the inhalation of sevoflurane in 100% oxygen with the maintenance of spontaneous ventilation. The administration of neuromuscular blocking agents (NMBAs) should be avoided until adequate bag-valve-mask ventilation is demonstrated. In our patient, inhalation induction was unremarkable with no evidence of upper airway obstruction; however, direct laryngoscopy revealed a grade II-III and indirect laryngoscopy was required to ensure optimal glottic visualization.

Cingi et al. reported their experience with general anesthesia and procedural sedation in 25 patients with MPS III during 94 anesthetic encounters.[10] None of the patients required an airway intervention or oxygen supplementation during sedation. Bag-valve-mask ventilation and endotracheal intubations were graded as easy in all cases. However, indirect video laryngoscopy was chosen as the primary airway management device in the majority of the encounters (n=68). Six (24%) patients had

postoperative airway problems including wheezing, croup or laryngospasm. A similar retrospective audit of anesthetic care for patients with MPS was undertaken by Frawley et al.[7] They identified a total of 43 patients with MPS III, of whom 34 required anesthetic care during a total of 86 procedures. Surgical procedures included dental extraction (34%), general surgical procedures (30%), and otolaryngologic procedures (26%). No problems were noted with bag-valve-mask ventilation. The Cormack-Lehane view during endotracheal intubation was grade 1 in 47 patients, grade 2 in 14 patients, Grade 3 in 1 patient, and grade 4 in I patient. There was 1 case of failed intubation. The patient were subsequently anesthetized by a different operator uneventfully at a later date. The authors noted that a difficult airway is unlikely when anesthetizing an MPS III patient although the risk does remain.

A final study evaluated changes in upper airway patency and oxygen saturation during procedural sedation.[11] A cohort of 25 patients (average age 6.9 years) required 43 episodes of sedation for 43 MRI and lumbar puncture. No patient failed sedation, required endotracheal intubation, or required prolonged use of an airway device. Although mask induction with sevoflurane was not problematic, airway obstruction was noted, requiring the application of continuous positive airway pressure, a temporary oral airway, jaw thrust, or shoulder roll in 14 of 43 procedures (33%). Although gas exchange improved once the sedation was transitioned from sevoflurane to propofol and/or dexmedetomidine. A small shoulder roll was needed to improve airway patency for 11 cases, while larger shoulder rolls tended to make the obstruction worse. Oxygen desaturation (≤ 90%) was noted during MR imaging in 3 of the 43 cases (7%). There was significant upper airway obstruction with the need to temporarily discontinue scanning during 2 cases (5%).

Airway concerns including a propensity for upper airway obstruction and difficulties with endotracheal intubation are magnified by the occurrence of cervical spine abnormalities in patients with MPS. Atlantoaxial subluxation due to odontoid hypoplasia and spinal cord compression due to spinal canal narrowing at the cervico-cranial and thoracolumbar regions have been reported.[12,13] In the absence of specific radiologic imaging, limitation of neck and cervical spine movement is suggested to avoid the potential for spinal cord injury. In our patient, we chose to stabilize the cervical spine with manual in-line stabilization during the initial attempt at directly laryngoscopy. These issues may complicate conventional direct laryngoscopy and mandate the need to consider alternative airway techniques for endotracheal intubation such as fiberoptic endotracheal intubation or indirect videolaryngoscopy.[14,15]

In addition to airway involvement, perioperative care may be impacted by primary respiratory involvement in patients with MPS. Respiratory involvement may include recurrent respiratory infections, upper and lower airway obstruction, tracheomalacia, restrictive lung disease, and sleep disturbances.[16] The study of Cingi et al. reported that 6 patients (24%) had postoperative airway problems including wheezing, croup or laryngospasm. Given these concerns, close postoperative respiratory monitoring may be indicated especially following prolonged procedures.

Infiltration of cardiac tissue is a frequent comorbid involvement of MPS including Sanfilippo syndrome. Frawley et al. reported cardiac involvement in 13 of the 34 patients in their cohort including 6 with valvular involvement, 6 with functional involvement, and 1 with conduction concerns.[7] As with other types of MPS, valvular involvement appears to be most common. In a longitudinal follow-up of 25 patients with MPS type III, no valvular stenosis or ventricular function abnormalities were noted.[17] During short-term follow up, patients demonstrated mild progression of abnormalities, none that required intervention. The authors concluded that the incidence of valvular disease was similar to MPS I and II, but was less severe. Given these concerns, preoperative echocardiography is warranted prior to anesthetic care.

All forms of MPS III show progressive neurodegeneration due to the accumulation of GAGs. However, MPS type III is distinct among the MPS as there may be a high prevalence of central nervous system (CNS) disease, with generally mild somatic manifestations.[18,19] Children with Sanfilippo syndrome may lose their intellectual functions, especially speech, before their motor function declines. Behavioral problems such as hyperactivity and irritability may become obvious earlier and are one of the more difficult aspects of the disorder to manage. Children with MPS III appear healthy at birth, but developmental delay or other behavior issues are usually evident by age 2-5 years. Mental and motor development peak by 3-6 years of age, after which intellectual decline usually occurs. Children with MPS type III often develop hearing or visual impairment loss.

Disturbances of coagulation function including thrombocytopenia or platelet dysfunction have been anecdotally reported in MPS patients.[20-22] Cohen et al. reported that 10 of the 34 MPS patients had evidence of clotting abnormalities including a mild prolongation of the clotting time in 5, thrombocytopenia in 3, and a low von Willebrand factor level in 2.[20] Others have reported posttonsillar hemorrhage related to platelet dysfunction.[22] Given these concerns, a careful history should be obtained regarding bleeding concerns especially mucosal membrane (epistaxis or gingival) bleeding suggestive of platelet dysfunction. Preoperative laboratory assessment of coagulation function may be indicated in major surgical procedures or those associated with significant blood loss.

In summary we present a 5-year-old child with MPS type III who required anesthetic care during adenotonsillectomy. MPS patients are at increased risk during anesthetic care or procedural sedation due to infiltration of airway structures which may lead to upper airway obstruction, difficulties with endotracheal intubation, excessive airway secretions, skeletal restriction of cervical spine movement, cardiac involvement, neurologic impairment, and frequent respiratory infections. End-organ involvement and the need for further evaluation should be identified during the preoperative history and physical examination. Ongoing clinical investigation is identifying novel treatments including gene therapy and enzyme replacement which may slow disease progression.

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