

ANESTHETIC MANAGEMENT IN A PEDIATRIC PATIENT WITH NOONAN SYNDROME, MASTOCYTOSIS, AND VON WILLEBRAND DISEASE: A CASE REPORT

Lynn Fitzgerald Macksey, CRNA, MSN
Holly Springs, North Carolina

Beth White, CRNA, MSN
Pittsburgh, Pennsylvania

This case report describes anesthetic considerations for a 6-year-old boy, admitted for adenoidectomy under general anesthesia, who had a complicated medical history, including mastocytosis, Noonan syndrome, and von Willebrand disease. Each affected the anesthetic plan and was addressed preoperatively among all surgical and anesthesia providers.

Mastocytosis created a major concern, with its increased numbers of histamine-filled mast cells. Each drug that was added or eliminated from the anesthetic plan, to prevent histamine release by the activation of triggers, was considered. Patient handling and temperature control were also concerns.

One of Noonan syndrome's characteristics is heart anomalies. This patient had a history of a patent foramen

ovale and pulmonary stenosis; therefore, air was carefully removed from all intravenous lines and syringes.

The main concern for bleeding difficulties was attributed to the history of von Willebrand disease, which results in prolonged bleeding time and can lead to delayed bleeding or serious postsurgical hemorrhage. Desmopressin was administered preoperatively to increase platelet aggregation and the von Willebrand factor level. The use of aspirin and other nonsteroidal anti-inflammatory drugs was avoided.

We discuss the clinical and anesthetic management of this case with a review of pertinent literature.

Key words: Anesthetic, Noonan syndrome, mastocytosis, pediatric, von Willebrand disease.

Multiple human dysmorphic syndromes were identified during the last century. Two syndromes, Noonan syndrome and Turner syndrome, have been closely associated because of similar characteristic facial features accompanied by short physical stature and congenital heart disease.

A clear distinction between Turner syndrome and Noonan syndrome was finally made when Ford et al,¹ in 1959, reported the karyotype 45X in a patient with the diagnosis of Turner syndrome. In 1963, Noonan and Ehmke² described 9 patients with a characteristic facies, valvular pulmonary stenosis, and short stature with normal chromosomes. Noonan syndrome is now

a well-characterized syndrome that exhibits specific facial characteristics (Table 1), along with a wide range of cognitive and physical hallmarks (Table 2).

Although a specific cause for Noonan syndrome is not known, the syndrome has a worldwide distribution, is panethnic, and affects males and females equally. The incidence range has been estimated from 1:1,000 to 1:1,250 live births.³

Table 1. Facial and cranial characteristics in Noonan syndrome

Hypertelorism
Downward eye slant
Ptosis
Epicanthal folds
Flat nasal bridge
Micrognathia
Posteriorly rotated ears
Large, acrocephalic head

Table 2. Physical and mental characteristics in Noonan syndrome

Short, webbed neck
Congenital heart disease; pulmonary stenosis most common
Short stature with long, thin limbs
Deafness
Bleeding diathesis
Mild mental retardation
Development delays
Delayed physical and sexual development
Hepatosplenomegaly
Scoliosis
Renal abnormalities
Hypertrophic osteoarthropathy with overriding digits

Autosomal dominant inheritance with variable expression has been well documented, but many cases seem to be sporadic.³ The fact that some children do not have a parent with Noonan syndrome likely reflects sporadic inheritance, that is, presumably the occurrence of a new mutation.⁴

There is no single treatment for Noonan syndrome, and treatment focuses on the problems that occur. Growth hormone has been used successfully to treat short stature. Surgical intervention may be required for severe cardiac anomalies. The cardiac abnormalities would be the primary concern when providing anesthesia to a patient with Noonan syndrome.

First described in 1869, mastocytosis is an uncommon disorder characterized by an abnormal accumulation of histamine- and heparin-containing mast cells. It can occur in 2 forms: (1) cutaneous and (2) systemic, which involves internal body organs. *Cutaneous mastocytosis*, also called *urticaria pigmentosa*, is the most common form and affects mostly children. In *systemic mastocytosis*, the presence of pathologic infiltrations of mast cells can occur in almost any organ, but the organs most commonly affected are bones, liver, spleen, lymph nodes, and peripheral blood.⁵

Symptoms of mastocytosis are related to the histamine released by mast cells, causing nausea and vomiting, itching, and skin lesions. Less frequent but more serious manifestations of histamine release include tachycardia, hypotension, peripheral and splanchnic vasodilation, acute bronchospasm, anaphylaxis, and shock. Heparin release from the mast cells can lead to decreases in the synthesis of clotting factors, which can produce a significant clinical coagulopathy.⁶

Triggers of the symptoms of mastocytosis include varied stimuli such as a mechanical irritation to the skin, psychological stress, temperature changes, alcohol ingestion, vomiting, exercise, and drugs (especially known histamine releasers).⁷ These triggers require careful anesthesia planning for preoperative, intraoperative, and postoperative management.

Case summary

A 6-year-old boy scheduled for adenoidectomy had a history of chronic nasal airway obstruction and sinusitis. He had a history of mastocytosis with multiple skin lesions, Noonan syndrome, a patent foramen ovale with pulmonary stenosis, and von Willebrand disease. The child did not have obvious physical characteristics of Noonan syndrome but did have cardiac anomalies. His parents said there was no developmental delay.

The patient weighed 16.3 kg. Known allergies included amoxicillin, codeine, intravenous (IV) dye,

and ibuprofen (Motrin). The only medication the child was currently taking was cetirizine (Zyrtec) for environmental allergies. To decrease the stress response, 8 mg of midazolam was given by mouth before the boy was brought to the preoperative area. Once in the preoperative area, an IV line was inserted, and 5 µg of IV desmopressin was given because of the history of von Willebrand disease, and 10 mg of IV diphenhydramine and 10 mg of IV hydrocortisone were given to block the uptake of histamine, decrease cell membrane permeability, and help decrease postoperative nausea and vomiting. The room temperature was warmed to 72°F, and a warming pad, placed on the operating table and under the bottom sheet, was turned on before bringing the child into the operating room.

On arrival in the operating room, a pulse oximeter, electrocardiographic monitor, and blood pressure cuff were applied. Initial vital signs showed a blood pressure of 112/80 mm Hg, a pulse rate of 90 beats per minute, a respiratory rate of 20 breaths per minute, and an oxygen saturation of 99%; the patient's skin temperature was 36.1°C. As prophylaxis for subacute bacterial endocarditis, 800 mg of IV ampicillin and 24 mg of IV gentamicin were given. A smooth inhalation induction was accomplished with a 60% nitrous oxide, 40% oxygen mixture, while sevoflurane was rapidly titrated from 2% to 8%. To blunt the sympathetic response to laryngoscopy, 50 mg of IV propofol and 25 µg of IV fentanyl were given. Known histamine-releasing drugs were avoided.

Intubation with a 4.5 cuffed oral RAE tracheal tube (Nellcor/Tyco Healthcare, Pleasanton, California) was uneventful after stage III anesthetic depth was obtained. Anesthetic depth was maintained with a nitrous oxide, 1 L oxygen, 1 L mixture and sevoflurane at 3% during the 30-minute case. The blood pressure was checked every 3 minutes to monitor for hypotension. Vital signs remained stable throughout the case. The patient was also closely monitored for flushing, hypothermia and hyperthermia, urticaria, bronchospasm, bleeding, and circulatory collapse. A precordial stethoscope was used continuously before induction through the recovery phase.

For antiemetic prophylaxis, 1.5 mg of IV ondansetron was given. The patient had received nothing by mouth since 3:00 AM, and the total fluid deficit was calculated to be 208 mL. Intravenous maintenance was calculated to be 52 mL/h. A total of 500 mL of lactated Ringer's solution was infused to combat the calculated fluid deficit and prevention of postoperative nausea and vomiting.

At the conclusion of the procedure, the patient was extubated and transferred to the recovery room. Vital signs on arrival were as follows: blood pressure, 114/36 mm Hg; pulse rate, 129 beats per minute; respiratory rate, 24 breaths per minute; oxygen saturation, 98% with “blow-by” oxygen; and temperature, 35.9°C. The child was responsive to voice and touch and had spontaneous ventilation and no audible stridor. No skin urticaria, mottling, blotching, or respiratory distress was noted. Recovery was uneventful. The child was observed for an additional hour and then was discharged home with his parents. Instructions were given to his parents to immediately contact the physician about any signs of breathing difficulty, hives, or bleeding.

Discussion

Patients with mastocytosis require special anesthetic preparation and consideration before induction, including pretreatment with histamine (H)₁ and H₂ antagonists, limiting stress and abrupt temperature changes, and avoiding histamine-releasing agents because all may cause mast cell degranulation (Table 3).

The preoperative administration of antihistamines may have prophylactic value in blocking tissue uptake of histamine; however, it does not affect histamine release from the mast cells themselves.⁸ Histamine release from mast cells can result in bronchospasm, skin flushing, and wheezing. Hypotension from peripheral vasodilatation can also occur, especially in a hypovolemic patient, leading to orthostatic hypotension. The effects of histamine can be minimized by slow opioid infusion, adequate IV volume and pretreatment with H₁ or H₂ antagonists. Nausea, vomiting, and retching related to stimulation of the chemoreceptor trigger zone (parasellar region in lateral medulla) caused by opioids are exacerbated by movement (stimulating vestibular apparatus of the ear).

The patient also had a history of von Willebrand disease, a hereditary bleeding disorder with a prolonged bleeding time and a mild to severe factor VIII deficiency. Anesthetic considerations preoperatively included treatment with desmopressin to help prevent bleeding. Desmopressin is a synthetic analogue of L-arginine vasopressin and causes a nonspecific augmentation of platelet function, resulting in increased platelet aggregation.

According to American Heart Association guidelines, the patient was at high risk for subacute bacterial endocarditis due to a patent foramen ovale and pulmonary stenosis. The suggested protocol details the use of ampicillin (pediatric dose, 50 mg/kg) with

Table 3. Histamine-releasing agents

Papaverine
Polymyxin
Thiamine
Quinine
Atropine and its derivatives
Gallamine
Dextran
Mivacurium
Atracurium
Opioids, including morphine sulfate, codeine, and meperidine
Thiopental
Curare
Aspirin and aspirin-containing agents

gentamicin, 1.5 mg/kg (for adults and children, not to exceed 120 mg) by the intramuscular or IV route within 30 minutes before starting procedure. Both of these antibiotics were infused before the start of the case.

Careful selection of preoperative, intraoperative, and postoperative pharmacologic agents should be exercised. Although true antibody-mediated allergic reactions are extremely rare, prevention and treatment of hemodynamic complications, specifically hypotension and shock, is the major concern in administering anesthesia to a patient with mastocytosis. Avoidance of stimuli and agents known to cause mast cell degranulation and subsequent release of histamine is essential. Inhaled anesthetics do not cause degranulation and may be safely used.⁹

If a muscle relaxant and a narcotic are required, the agents recommended are succinylcholine (administered by bolus IV injection or by intermittent drip) and meperidine, respectively. If these agents can be avoided, it is prudent to do so.⁹ In our case, a muscle relaxant was not required, and fentanyl, a non-histamine-releasing opioid, was used.

Management of severe hypotension and shock follows standard resuscitation principles, including volume support and the use of α and β agents. Hydrocortisone, 10 mg IV, was given according to the anesthesiologist's order, although steroid preparations have not been shown to be of value.⁸

Hemorrhagic diathesis secondary to heparin release from mast cells is a potential concern, although it is uncommon. Protamine sulfate has been used successfully for this condition and was available. The patient

also had von Willebrand disease, which further complicated anesthetic management. Desmopressin was given preoperatively in an effort to prevent potential bleeding.

Summary

We describe a 6-year-old boy with mastocytosis and Noonan syndrome further complicated by von Willebrand disease and cardiac anomalies who was undergoing general anesthesia for an adenoidectomy. Problems, precautions, and pharmacologic agents associated with the anesthetic management of the patient were reviewed. The patient's induction, maintenance, and emergence were uneventful.

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AUTHORS

Lynn Fitzgerald Macksey, CRNA, MSN, is a staff nurse anesthetist at Critical Health Systems group and WakeMed Hospital in Raleigh, NC. Email address: LynnMacksey@msn.com.

Beth White, CRNA, MSN, is a staff nurse anesthetist at the University of Pittsburgh Physicians Anesthesia group and University of Pittsburgh Medical Center Shadyside Hospital in Pittsburgh, Pa. Email address: beth1302@excite.com.