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Anesthesia and the Lesch–Nyhan Syndrome

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The Lesch–Nyhan syndrome, a genetically determined disorder of purine metabolism, was first definitively described in 1964.[1] It is an X-linked recessive disorder that occurs exclusively in males. Biochemically the primary defect is almost entire absence of hypoxanthine–guanine–phosphoribosyltransferase (HGPRT) activity, leading to excess purine production, and elevation of uric acid concentrations throughout the body. Clinically, patients are usually mentally subnormal, with a characteristic pattern of compulsive self-mutilation, spasticity, and choreoathetosis. The hyperuricemia is associated with nephropathy, urinary tract calculi, arthritis, and tophi. Comprehensive reviews of the syndrome have been published.[2,3] The incidence is in excess of 5.2 cases per million male births, and life expectancy is shortened, with many patients dying of renal failure within 20 years.[3] Because of the high incidence of calculi, patients may present for surgery of the urinary tract, orthopedic surgery, or other unrelated surgical problems. There are no reports describing anesthetic management. We describe such a case and discuss the potential anesthetic problems, which include major abnormalities of cardiorespiratory, renal, and nervous system function.

Report of a Case

A 23-year-old man with Lesch–Nyhan syndrome diagnosed at one year of age was admitted for treatment of partial right ureteral obstruction due to calculi in the right renal pelvis. The history obtained was poor but notably included recurrent chest infections with the last documented occurrence 6 months before admission and an absence of any seizure disorder. A cystoscopy and right retrograde pyelogram had been performed 2 weeks before admission at another hospital, and total dental extraction had been performed at age nine to prevent further self-mutilation. No information about these anesthetics was available: they were apparently uneventful. Physical examination revealed subnormal mentation and evidence of previous self-mutilation of the upper lip and hands. Although the patient would not cooperate with a detailed examination of his oro-pharynx, we were able to note the absence of a substantial portion of his upper lip, areas of perioral scarring, the absence of dentition, and a large scarred tongue that appeared to fill his entire oral cavity when the mouth was closed and also appeared to partially occlude the airway when the patient was supine. Vital signs on admission were heart rate 80 bpm, arterial blood pressure 120/80 mmHg, temperature 37° C, and respirations of 12 breaths/min. Chest roentgenogram revealed no cardiopulmonary abnormalities, and electrocardiogram showed only a sinus tachycardia. Laboratory tests revealed: hematocrit 40%, hemoglobin concentration 14 g/dl, uric acid 0.38 mmol/l (6.4 mg/dl) (normal 0.16–0.47 mmol/l), and potassium 5.1 mmol/l. Creatinine clearance was 69 ml/min (normal 75–125 ml/min). Medication taken by the patient prior to admission included diazepam 5 mg three times a day. He was scheduled for percutaneous renal stone removal and cystoscopy under general anesthesia.

The patient was brought to the operating room 90 min after receiving diazepam 10 mg, po. An inhalation induction with isoflurane and oxygen was accomplished with spontaneous ventilation. After it was established that a satisfactory airway could be maintained via mask ventilation, tracheal intubation was performed following administration of atracurium 30 mg iv. Anesthesia was maintained with isoflurane in a mixture of 70% N_2O and 30% O_2, while paralysis was maintained with intermittent iv injections of atracurium. During the 4 h of anesthesia, the patient's condition was stable with arterial blood pressure, ranging between 90–110 mmHg systolic and 40–50 mmHg diastolic. Heart rate ranged from 80 to 90 bpm. At the end of the procedure, neuromuscular blockade was reversed with atropine 1.2 mg and neostigmine 2.5 mg iv, and the inhaled anesthetics were discontinued. Adequate spontaneous respirations resumed, and the trachea was extubated. The patient was transferred to the recovery room, where his recovery from anesthesia was uneventful. He was discharged after 10 days without evidence of anesthetic complications.

Discussion

Patients with Lesch–Nyhan syndrome present three types of problems of concern to the anesthesiologist. First, there are the functional disturbances created by

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the disorder; second, there are concerns about the metabolism and excretion of any drugs that may be administered; and, third, there are potentially significant abnormalities of neurochemical function.

The self-mutilation usually involves trauma to perioral tissue,[2] and subsequent scarification may suggest the likelihood of difficulties with endotracheal intubation. A review of the pertinent literature reveals that regurgitation and vomiting occur frequently in Lesch–Nyhan syndrome. Apparently no mechanism has been found to explain this characteristic of the syndrome. Because athetoid dysphagia is also characteristic of the syndrome, aspiration pneumonia often follows episodes of vomiting.[2] Preoperatively, consideration might be given to the use of metaclorprimide to promote gastric emptying and certainly to the use of an H_2 receptor blocker such as ranitidine in an effort to elevate gastric pH above 2.5. Although our patient had none, seizure disorders have been associated with Lesch–Nyhan syndrome.[2] The need for restraints to prevent mutilation, the limited mental function and spastic musculoskeletal abnormalities make positioning the patient and placement of iv lines difficult.[2] The patients are frequently malnourished[2] and may have renal functional impairment.[5] Drug therapy will commonly include a benzodiazepine.[6] Hypertension or coronary artery disease may be found in association with the hyperuricemia.[7]

The choice of anesthetic agents will be influenced by the results of preoperative assessment, the surgical problem, the primary metabolic defect, and the degree of renal impairment. Although none of the widely used inhaled anesthetics are known to have metabolic pathways involving HGPRT, the minimal overall metabolism, and absence of nephrotoxity probably make isoflurane the preferred anesthetic.[7] The metabolism of thiopental, methohexital,[8] ketamine, or etomidate[9] should not be affected by abnormality in HGPRT function. The use of succinylcholine may be precluded by concern about abnormal potassium flux in association with the spastic muscle disorder.[10] Because it is eliminated by Hoffman degradation, atracurium appears to be the logical choice of muscle relaxant for use in patients with the Lesch–Nyhan syndrome.[11]

Complex, and as yet ill understood, abnormalities of adrenergic responses have been found in association with this syndrome. Reduced monoamine oxidase activity has been reported.[12] Plasma dopamine hydroxylase, the enzyme responsible for catalyzing the conversion of dopamine to norepinephrine, and cited as an index of adrenergic function,[13] has been reported to have both increased[13] and reduced[14] activity in Lesch–Nyhan syndrome patients. There is, however, agreement that the adrenergic pressor response to stress is absent[13,14] and that the cholinergic nervous system is responsible for heart rate control under stress.[14] As it is not known whether the lack of stress response represents a presynaptic or receptor defect,[13] all exogenous catecholamines should be administered with great caution. Similarly, it would be prudent to avoid administering drugs known to produce adverse reactions in patients with inhibited monoamine oxidase activity.[15] There is increasing evidence of involvement of purines in neurochemical function, especially the dopaminergic system, benzodiazepine receptors, and central morphine activity.[17]

The movement disorder of the Lesch–Nyhan syndrome suggests involvement of the basal ganglia areas, which normally contain higher levels of hypoxanthine–guanine–phosphoribosyltransferase than other areas of the brain. Since caffiene, which can elicit self-mutilation in animals, can also inhibit the binding of diazepam to its receptors, it has been proposed that the diazepam-binding site may in some way be involved in causing some of the bizarre behavioral manifestations of the Lesch–Nyhan syndrome. Because there is evidence that at least some of the central effects of morphine may be secondary to morphine-induced release of the purine adenosine, the defect in purine metabolism of the Lesch–Nyhan syndrome may modify the effects of exogenously administered morphine.[17] It is tempting to speculate that further understanding of the defect underlying Lesch–Nyhan syndrome will lead to greater understanding of fundamental neurochemical function, progress of obvious relevance for anesthesiology.

In conclusion, despite what may initially appear to be an almost overwhelming set of preoperative problems, there are few contraindications to the use of standard anesthetic techniques, and anesthesia may be, as in our case reported above, surprisingly uneventful.

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Postoperative Rigidity Following Sufentanil Administration

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Chest wall rigidity after administration of narcotics first was reported by Hamilton and Cullen[1] in 1953. Morphine,[2] meperidine,[3] fentanyl,[8–5] fentanyl–droperidol[3] (Innovar®), and sufentanil[5] can produce decreased chest wall compliance and ventilatory difficulty. Following high-dose fentanyl (70–115 μg/kg), chest wall rigidity may occur several hours after surgery.[6] We report a patient in whom chest wall rigidity developed in the recovery room 3 hrs after administration of 4 μg/kg of sufentanil.

REPORT OF A CASE

A previously healthy 36-year-old, 75-kg ASA physical status I man was scheduled for an elective lumbar laminectomy for disc herniation. He was premedicated with hydromorphone 1 mg and scopolamine 0.43 mg im, and on arrival to the operating room was awake and cooperative. Awake endotracheal intubation was accomplished after topical application to the tongue and hypopharynx of lidocaine 10% spray, bilateral superior laryngeal nerve blocks with lidocaine 4%, and 4 ml intratracheal lidocaine 4% under direct vision. Diazepam 5 mg iv in divided doses was required for additional sedation during the intubation. Sufentanil 0.5 μg/kg (37 μg) iv was then given to provide analgesia for bladder catheterization, during which the patient was somnolent, spontaneously ventilating, and analgetic.

After insertion of the Foley catheter, the patient was easily aroused. He was able to move himself onto the operating room table into the prone position and then gave the "thumbs-up" sign. General anesthesia was induced with sufentanil 3.5 μg/kg (263 μg) and pancuronium 5 mg iv and maintained with nitrous oxide/oxygen 70/30%. Surgery proceeded uneventfully; additional pancuronium 2 mg was given 1 h before the end of surgery. The operation concluded 2.5 h after the induction dose of sufentanil; no additional narcotic had been given since induction. Following iv administration of neostigmine 3.5 mg, physostigmine 1 mg, and glycopyrrolate 0.4 mg iv, the patient was awake and alert. Sustained tetanus (100 Hz) was demonstrated with a peripheral nerve stimulator. His vital capacity was 700 ml, and his respiratory rate was 12 breaths/min. He was strong enough to lift himself above the Wilson frame for 10 s, and after he turned to the supine position, his trachea was extubated. Immediately after extubation he was alert and asked questions about his surgery. In the recovery room, BP was 156/80 mmHg, HR 70 bpm, respiratory rate 12 breaths/min, and temperature was 35.2° C. His ventilation was judged to be "adequate" by the recovery room personnel, and cyanosis was not evident. Oxygen, 5 l/min was administered via nasal cannula. At no time was any narcotic or narcotic antagonist administered.

Over the next 22 min his respiratory rate and depth gradually decreased until he required verbal stimulation to breathe. His blood pressure was 120/80 mmHg, and his heart rate was 68 bpm. He then became rigid, cyanotic, and unresponsive. It was impossible to open his mouth or to ventilate him by mask, even with a nasal airway in place. He was given succinylcholine 100 mg iv, and within seconds his chest wall compliance increased. His trachea was reintubated, and, although arousable, he was somnolent. His ventilation via T-piece was inadequate, due to insufficient effort, and mechanical ventilation was required for three additional hours. During this time he exhibited strong hand grip, sustained head lift and arousal with stimulation. Arterial blood gas (ABG) before the second extubation (30 min while breathing through a T-piece with an O_2 flow rate of 6 ls/min) showed pH_a 7.37, Pa_{O_2} 130 mmHg, Pa_{CO_2} 48 mmHg, and base excess +2 mEq/1. Although still somnolent, his ventilation had improved; after extubation his arterial pH_a was 7.36, Pa_{CO_2} 48 mmHg, Pa_{O_2} 135 mmHg, and base excess +1.9 mEq/l. His first requirement for analgesic medication was 15 h postoperatively.

DISCUSSION

Chest wall rigidity during narcotic administration, whether for small doses used for sedation or large doses used for anesthetic induction, is not uncommon. The incidence, however, is disputed. Lunn *et al.*[7] either failed

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