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Anesthetic management of renal transplantation in a patient with familial dysautonomia

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Abstract
Familial dysautonomia is an inherited disorder characterized by autonomic and sensory nervous system neuropathy resulting in extremely labile blood pressure (severe hypertension followed by hypotension). As more patients with familial dysautonomia reach adulthood due to improved medical treatment, perioperative encounters of patients with familial dysautonomia will increase. This report is the first adult case to describe an anesthetic management of kidney transplantation for an adult familial dysautonomia patient. The clinical manifestations of this disease and rationale of our anesthetic management are discussed.

Key words Adrenergic receptor · Blood pressure · Familial dysautonomia · Kidney

Introduction

Familial dysautonomia, also known as Riley-Day syndrome or hereditary sensory and autonomic neuropathy type 3, is an inherited disorder affecting primarily individuals of Ashkenazi/Eastern European Jewish descent in an autosomal recessive fashion, causing incomplete neuronal development, as well as neuronal degeneration within the peripheral and autonomic nervous system [1–4]. The carrier frequency in Jewish individuals of Eastern European (Ashkenazi) ancestry is about 1/30, while the carrier frequency in non-Jewish individuals is about 1/3000 [1,2]. Signs of this disorder are usually present at birth and increase with age. Familial dysautonomia is associated with high morbidity and mortality; however, with improved medical care, patients are surviving into adulthood. A few decades ago, 50% of patients with familial dysautonomia died by age 5 years, while more recently it has been noted that a patient with this condition has a 50% probability of reaching the age of 40 [1,2]. This disorder provides significant anesthetic challenges affecting multiple organ systems.

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Case presentation

This case involves a 27-year-old male patient with familial dysautonomia presenting for living-related kidney transplantation. Our patient developed end-stage renal disease with biopsy-proven glomerulosclerosis. The patient's creatinine rose to 7.5 $mg \cdot dl^{-1}$ preoperatively and he received trice-weekly hemodialysis. The patient was admitted the day prior to surgery for hemodialysis. The patient has significant other comorbidities that are common and related to his primary disease, including reactive airway disorder, restrictive respiratory insufficiency with frequent pulmonary infections and requirement of positive airway pressure to maintain adequate (>90%) oxygen saturation at night, developmental delay, seizure disorder, bipolar disorder, scoliosis, recurrent syncopal episodes due to orthostatic hypotension and bradycardia, and complete atrioventricular (AV) block requiring pacemaker insertion. The patient also had undergone two Nissin fundoplication procedures to control gastroesophageal reflux and a gastrostomy tube placement for nutritional supplementation. The medications included clonidine, amlodipine, propranolol, albuterol, montelukast, divalproex sodium, ziprasidone, escitalopram, and lansoprazole.

On the morning of the surgery, the electrophysiology service reprogrammed the pacemaker [from Synchronous Dual Chamber (DDD) to Fixed Rate Dual Chambe (DOO) at the rate of 75 $\cdot$ min^{-1}], and his routine antianxiety medications were administered. The patient's preoperative vital signs were significant for oxygen saturation of 85%-90% (on 4 $l \cdot min^{-1}$ nasal oxygen) and blood pressure (BP) of 175/126 mmHg. In the operating room (OR), standard American Society

of Anesthesiology (ASA) monitors were applied and his head was elevated to ~30° in order to prevent the aspiration of gastric contents. In order to blunt the sympathetic outflow-mediated lability in blood pressure, dexmedetomidine infusion i.v. was started at 0.7 μg·kg^{-1}·h^{-1}. A radial arterial line was placed and the patient was hydrated with 1 l of lactated Ringers solution prior to induction. Given the significant aspiration risk, rapid sequence induction was carried out with cricoid pressure in the head-up position with propofol 150 mg i.v. and succinylcholine 120 mg i.v. followed by midazolam 2 mg i.v. and fentanyl 150 μg i.v. after intubation. A right internal jugular double-lumen central line was placed post induction to infuse vasoactive drugs and to monitor central venous pressure (CVP). Initial CVP was noted to be 6–8 mmHg (despite pre-induction hydration), likely due to relative intravascular hypovolemia secondary to chronic hypertension in this patient, as well as the symptoms associated with familial dysautonomia. Immediately after intubation, the patient's BP increased to 190–210/120–130 mmHg from pre-induction BP of 150–160/120–130 mmHg. Midazolam 3 mg i.v., as well as additional divided doses of fentanyl 850 μg i.v. (for a total of 1 mg i.v.) was given with minimal BP change. Nitroprusside infusion was started at 0.2 μg·kg^{-1}·min^{-1}. Blood pressure slowly decreased over the next 5 min to 150 s/100 s mmHg. Care was taken to protect the eyes with an artificial tear preparation (lacrilube) and tape, given the higher risk of corneal injury due to lack of tear production and corneal insensitivity seen in familial dysautonomia. A bispectral (BIS) monitor was placed and the score titrated between 35 and 45. Anesthesia was maintained on sevoflurane at 0.7–0.8 minimum alveolar concentration (MAC) and dexmedetomidine infusion was continued at 0.7 μg·kg^{-1}·h^{-1} throughout the procedure. The patient's vital signs were stable throughout the procedure with minimal anesthetic adjustment.

At the end of the surgery, the patient was extubated in the OR with head elevated 30° to decrease the risk of aspiration. In addition, dexmedetomidine was continued at a lower dose (0.2 μg·kg^{-1}·h^{-1}) in order to decrease the stress of extubation from triggering a crisis episode. Paralytics were not administered for the last more than 1 h to minimize the risk of residual weakness. During the emergence, the patient's BP paradoxically decreased and he required small doses of phenylephrine (20 μg i.v.) as the BP drifted down to the range of systolic blood pressure (SBP) ~110 mmHg. It was noted that a relatively small dose of phenylephrine (20 μg) produced an exaggerated response, bringing the SBP back to the 150- to 160-mmHg range. Muscle relaxant reversal (neostigmine 0.05 mg·kg^{-1} i.v. with glycopyrrolate 0.01 mg·kg^{-1} h^{-1} i.v.) and antiemetic (ondansetron 4 mg i.v.) was given. Postoperatively patient was brought to the postanesthesia care unit (PACU) on dexmedetomidine infusion (0.2 μg·kg^{-1}·h^{-1}) in a stable condition.

In the PACU, postoperative pain control was started using hydromorphone boluses (0.2–0.4 mg i.v. per 1dose q 10 min), and patient-controlled analgesia (PCA) hydromorphone i.v. was started (0.2 mg i.v. q 10 min; maximum 1.2 mg·h^{-1}). After the PCA was started, dexmedetomidine infusion was discontinued. Vital signs in the PACU remained stable. BP ranged in the100–140/60–90s mmHg; heart rate (HR) was 70 bpm (paced); respiration rate (RR), 12–14 breaths·min^{-1}; saturation 96%-98% on nasal oxygen of 3–5 l·min^{-1}; and CVP, 7–8 mmHg. Intravenous fluid in the PACU ranged between 500 and 600 ml·h^{-1}, including thymoglobulin infusion [½ Normal Saline (NS)], bicarbonate infusion (½ NS), with NS and Lactated Ringers (LR) boluses administered as needed. Urine output in the PACU ranged from 400 to 500 ml·h^{-1}, likely in the post-transplant diuretic phase. The patient stayed stable during the immediate postoperative period.

The patient's hospital stay was complicated by respiratory failure secondary to aspiration, requiring intubation and Surgical Intensive Care Unit (SICU) transfer on postoperative day (POD) 4. The patient's condition improved and he was extubated on POD 6, and transferred out of the SICU on POD 9. The patient was discharged from the hospital on POD 14.

Discussion

This is the first case report to describe the anesthetic management for an adult patient with familial dysautonomia undergoing renal transplantation. The patient presented with multiple anesthetic challenges in addition to his end-stage renal disease. This patient had developed end-stage renal disease with biopsy-proven glomerulosclerosis. Renal failure is a frequent complication of familial dysautonomia due to (1) autonomic denervation of renal arteries with subsequent loss of renal blood flow autoregulation and (2) repeated, paroxysmal, and exaggerated hypertensive episodes.

Patients with familial dysautonomia present with several significant anesthetic management challenges due to severe autonomic dysfunction resulting in hemodynamic instability and esophageal dysmotility, causing increased aspiration risk [2,4,5]. The prevention of dysautonomic crises, triggered by mild events, including pain and emotional stress, is critical for this patient population. Dysautonomic crises present as episodes of exaggerated tachycardia or bradycardia, hypertension or hypotension, vomiting, and profuse sweating [3,4]. Patients with familial dysautonomia can also have other multisystem involvements including orthostatic hypotension, abnormal pain perception, AV conduction

disturbances and QT interval prolongation, corneal insensitivity/lacrimal disorder, erratic temperature control, baroreceptor/chemorecepter dysfunction, restrictive lung disease secondary to scoliosis, electrolyte/fluid disturbances, and glomerulosclerosis, all of which will affect pre-, intra-, and post-anesthetic management [2–6]. Certain clinical manifestations of this disorder predispose patients to operative procedures, such as gastrostomy tube insertion for nutrition supplementation, scoliosis correction (up to 90% of those with this disorder suffer from scoliosis), and Nissin fundoplication to reduce aspiration risks.

The lack of autonomic nerve terminals in the blood vessels and catecholamine receptor upregulation results in severe hemodynamic instability and extreme sensitivity to both endogenous and exogenous vasopressor agents [2,3]. These patients have reduced production of endogenous catecholamines with heightened receptor sensitivity, and even a small release of catecholamines can result in an exaggerated blood pressure (BP) and heart rate (HR) response. We observed that our patient displayed significant hypertension during induction, and paradoxical relative hypotension (despite reduction in anesthetic depth) during emergence. Moreover, a small dose of phenylephrine (20 μg) produced profound increases in BP. The presentation of hemodynamic instability in patients with familial dysautonomia can vary greatly, including orthostatic hypotension, which may occur without reflex tachycardia; and supine hypertension and bradycardia, which may lead to asystole and complete AV block requiring a pacemaker. We chose to start dexmedetomidine infusion immediately upon the patient's arrival at the OR. Dexmedetomidine, a selective alpha 2 agonist, was chosen as it has dose-dependent sedative/anxiolytic properties, as well as some opioid-sparing analgesic effects, with minimal respiratory compromise. More importantly, dexmedetomidine blunts catecholamine release from the central nervous system, thereby decreasing the possibility of crisis trigger while providing hemodynamic stability [7]. In addition, dexmedetomidine infusion enhances the urine flow rate and perioperative renal function in patients susceptible to developing acute kidney injury [8], perhaps via the enhancement of renal blood flow [9]. Low-dose dexmedetomidine infusion was continued during emergence to reduce the risk of triggering a crisis episode. Sevoflurane was chosen for maintenance of anesthesia because it allows rapid titration, as adjustment of depth of anesthesia can help the control of labile BP. A BIS monitor was placed to monitor the level of anesthesia, as hemodynamic change was felt to be unreliable in determining anesthetic depth, given the autonomic dysfunction/dysautonomic crisis episodes. The use of fluid boluses is preferred over vasopressors, as the upregulation of catecholamine receptors in patients with familial dysautonomia makes titration of vasopressors difficult [2–5]. We used lactated Ringers solution and 5% albumin for fluids, targeting stable hemodynamics with CVP 10–15 mmHg during the procedure. If vasopressor infusions are necessary, careful titration will be important, starting at a very low dose, as an exaggerated response is expected.

Autonomic dysmotility commonly affects the gastrointestinal system in patients with familial dysautonomia. Esophageal dysmotility results in difficulty in swallowing, leading to failure to thrive, and patients with familial dysautonomia frequently require a gastrostomy tube for nutritional supplementation. The abnormal esophageal motility also leads to increased gastroesophageal reflux, which often requires medical treatment, as well as a Nissin fundoplication [3]. The increased risk of reflux, along with the vomiting episodes associated with dysautonomic crises, increases the risk of aspiration. Given these risks, rapid sequence induction was performed with the patient's head elevated at 30° until the moment of intubation, to reduce the aspiration risk, given the patient's increased risk of reflux and vomiting risk with crises. Likewise, extubation was performed with patient again in the head-up 30° position and fully awake to reduce the aspiration risk. Elevation of the upper body is also useful in avoiding supine hypertension in these patients.

The respiratory system can be compromised by this disorder in several ways. First, frequent microaspirations at night result in recurrent respiratory infections and pneumonia. Second, up to 90% of patients with familial dysautonomia develop scoliosis, which, in severe cases, may lead to restrictive lung disease [3,4]. Patients with familial dysautonomia are thought to have chemoreceptor and baroreceptor dysfunction due to autonomic dysfunction [3,5]. This leads to an increased incidence of central sleep apnea and breath-holding, as well as lower oxygen saturation and higher carbon dioxide levels in these patients. As expected, our patient had a somewhat delayed return of spontaneous respiration, likely attributable to autonomic chemoreceptor and baroreceptor dysfunction [2–6]. As mentioned earlier, this patient's in-hospital course was complicated by a temporary need for ventilator support later in the postoperative period.

Patients with familial dysautonomia are often chronically dehydrated due to sweating, vomiting, and decreased oral intake [3]. Extreme sweating and vomiting can lead to electrolyte disturbance (e.g., hyponatremia). Hypovolemia should be corrected to limit hemodynamic instability during the induction as well as maintenance of anesthesia.

Patients with familial dysautonomia are thought to have decreased pain perception [2,3]. Corneal insensitivity along with lacrimal disorder increases the risk of

corneal abrasion, even in the awake state [3,6]. However, pain control is important, as these patients are thought to have intact visceral and peritoneal pain perception. Pain, if untreated, can be a trigger for dysautonomic crises.

Proper body temperature regulation can also be a problem in this patient population. This can lead to erratic body temperature at baseline as well as erratic febrile response. For example, a marked increase in temperature can be triggered by minor infections, while a major infection may not trigger a febrile response [2–4]. This can make perioperative temperature regulation a challenge, as well as detecting signs of infection (fever) postoperatively more difficult.

In summary, anesthetic management in a patient with familial dysautonomia is a challenge. With improved medical care and the survival of patients with familial dysautonomia improving, we will have more opportunity to care for these patients reaching adulthood.

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