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Perioperative care of a child with a germline mutation in succinate dehydrogenase complex, subunit B (SDHB) presenting with synchronous functional paragangliomas in thorax and pelvis

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Keypoints

Anesthetic management of patients with functional paragangliomas can be challenging. The anesthesiologist must anticipate the potential for significant changes in hemodynamics during the perioperative period and be prepared to treat them accordingly. Preparation should include placement of adequate vascular access with consideration of invasive blood pressure monitoring and central venous access as well as ensuring the availability of inotropic agents, vasopressors, beta-blockers and vasodilators. The occurrence of synchronous paragangliomas is uncommon, but may be encountered in patients with germ-line mutations.

Abstract

Paragangliomas can either occur sporadically or be associated with a number of germline mutations. Optimal management includes complete surgical resection. Depending on whether the paraganglioma is comprised of functional (catecholamine-secreting) or non-functional neuroendocrine tissue, perioperative care becomes a major consideration. Significant hemodynamic perturbations secondary to catecholamine release can occur during multiple steps in the procedure such as laryngoscopy or tumor manipulation, and require close monitoring and intervention with vasoactive substances. We describe the perioperative care of a child with a succinate dehydrogenase complex, subunit B (SDHB) germline mutation who presented with synchronous functional paragangliomas located in the thorax and pelvis.

Keywords: Paraganglioma, succinate dehydrogenase, catecholamines, hemodynamics, perioperative care, germ-line mutation.

Introduction

Paragangliomas are tumors that arise from neuroendocrine tissue and can be traced back to cells from the neural crest. They can originate from the sympathetic nervous system positioned symmetrically along the paravertebral axis or from the parasympathetic nervous system, predominantly represented by the vagus nerve and its extensions.[1] If the neuroendocrine tissue tumor is located in the adrenal gland, the term pheochromocytoma is applied.[2] Sympathetic paragangliomas tend to hypersecrete catecholamines (epinephrine, norepinephrine, dopamine) while parasympathetic paragangliomas are often non-secretory.

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About 60% of paragangliomas and pheochromocytomas occur sporadically, whereas 40% are associated with a germline mutation in one of the susceptibility genes identified so far.[3] Examples include multiple endocrine neoplasia type 2 (*RET* gene), von Hippel-Lindau disease (*VHL* gene), neurofibromatosis type 1 (*NF1* gene), familial pheochromocytoma (*TMEM127* or *MAX* genes), polycythemia paraganglioma syndrome (*EPAS1* gene) or Reed syndrome (*FH* gene). [3,4] A more recently discovered disease entity called familial paraganglioma-pheochromocytoma syndrome is associated with mutations in the succinate dehydrogenase (*SDH*) gene. Succinate dehydrogenase, also known as succinate-coenzyme Q reductase (SQR) or respiratory complex II, is an enzyme complex located in the inner mitochondrial membrane. It consists of four subunits (SDHA, SDHB, SDHC and SDHD) and participates in the electron transfer chain and citric acid cycle (oxidation of succinate to fumarate).

A fifth gene, *SDHAF2* (also known as *SDH5*), encodes a protein required to support the function of the SDHA subunit. Mutations in those genes impair the function of the SQR/ respiratory complex II. This results in accumulation of large amounts of succinate. Succinate functions as a competitive inhibitior of 2-oxoglutarate-dependent dioxygenases (Jumonji histone demethylase, TET [ten eleven translocation] hydroxylase) that are involved in regulation of the epigenome.[3]

Patients with mutations in one of the abovementioned five genes collectively referred to as the *SDHx* genes are at risk of developing paragangliomas and require lifelong surveillance in the form of physical examination, imaging and biochemical testing.

Treatment involves surgical removal to prevent complications such as mass effect, malignant transformation and catecholamine hypersecretion which may lead to either acute hypertensive crises or chronic hypertension. First-degree relatives of an individual with known *SDHx* gene mutation should be offered molecular testing since inheritance of this mutation occurs in an autosomal dominant fashion.

We discuss the anesthetic management of a child diagnosed with synchronous paragangliomas in the thoracic paraspinous region and the bladder.

Case report

An 11 year-old boy presented for resection of synchronous paragangliomas located in the bladder and thorax. The lesions were discovered during surveillance scans. The patient's father was a known carrier of a specific *SDHB* mutation (C.605_609 dupaCGGA) after being diagnosed with gastrointestinal stromal tumor as a young adult. Given this history, the family decided to proceed with genetic testing for the patient who was found to also carry this specific mutation. Subsequently, the patient underwent biochemical testing and a whole-body magnetic resonance imaging scan. Biochemical testing showed elevated levels of chromogranin A (118 ng/mL, reference range: 0-95 ng/mL), norepinephrine (2791 pg/mL, reference range: 85-1250 pg/mL) and normetanephrine (3.27 nmol/L, reference range: 0-0.89 nmol/L). Epinephrine levels were within normal limits (138 pg/mL, reference range 18-460 pg/mL). Dopamine could not be determined due to insufficient sample size but was within normal limits during testing three months earlier. The magnetic resonance imaging study revealed three distinct lesions: 1) a subcentimeter, T2 hyperintense lesion in the right femoral neck; 2) a small (1.9 x 1.4 x 1.1 cm) anterior spinal mass at T10 (Figure 1a and b); and 3) a small (1 cm) lesion arising from the right bladder base (Figure 1 c and d). The lesion in the femoral neck was determined to be non-specific and unrelated to the other masses. A I-123 metaiodobenzylguanidine (MIBG) scan with single-photon emission computed tomography showed no other evidence of MIBG-avid disease. The patient's only other health issue included prematurity (born at 34 weeks of gestation) with subsequent need of brief respiratory support in the neonatal intensive care unit. He had undergone une-

ventful surgery with general anesthesia once for tonsillectomy and adenoidectomy. He had no known drug allergies and was taking cetirizine for seasonal allergies. His review of systems was negative for palpitations, dizziness, diaphoresis, anxiety attacks, dyspnea, syncope, diarrhea, chest pain, abdominal pain or nausea/ emesis.
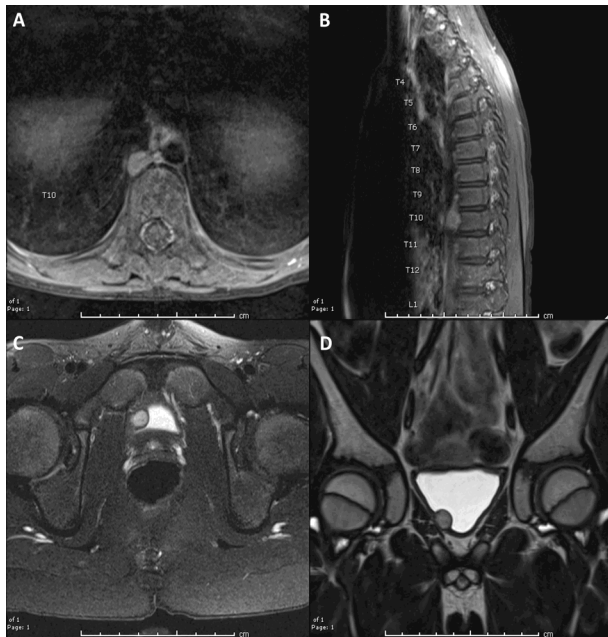

Figure 1 (a-b/c-d). Whole-body magnetic resonance imaging scan. Paraganglioma located in paraspinal area at T10 level displayed in A) sagittal and B) axial views. Paraganglioma of the bladder base displayed in C) axial and D) coronal views.

Prior to the procedure, the patient was admitted to the intensive care unit for initiation of α-blockade with prazosin and intravenous fluid hydration. Before anesthetic induction, the patient's vital signs were within normal limits (Temperature 36.7°C, heart rate 78/min, blood pressure 102/56 mmHg, respiratory rate 12/min, oxygen saturation 99% on room air). A 22G peripheral intravenous catheter in the left arm was used for premedication with 2 mg midazolam. After arrival in the operating room and placement of standard ASA monitors, induction of general anesthesia was achieved with 4 mg midazolam and 15 mcg sufentanil. Bag-mask ventilation was easy. After deepening the anesthetic plane with sevoflurane and muscle relaxation with 4 mg vecuronium, a 26 French left-sided double lumen endotracheal tube

was placed via direct laryngoscopy (Macintosh 3 blade, Cormack and Lehane grade 1 view). Positioning was confirmed by fiberoptic bronchoscopy. The patient's vital signs remained stable during the induction period. After securing the airway, additional vascular access was obtained (two additional large-bore peripheral intravenous catheters, 20G left radial arterial line, right internal jugular triple-lumen central venous line).

Anesthesia was maintained with isoflurane (end-tidal concentration 0.6-0.8%), sufentanil (0.2-0.3 mcg/kg/h) and intermittent boluses of sufentanil and vecuronium. For the first part of the procedure, the patient was positioned in left lateral decubitus position. The right lung was isolated for video-assisted thoracoscopy. After localization of the paraspinal lesion, which was attached to the large sympathetic chain (Figure 2), resection was attempted. Upon manipulation of the mass, the systolic blood pressure increased from a baseline of 80-90 mmHg to around 140 mmHg and reflex bradycardia was noted with a heart rate drop from baseline 70-80s/min to 40/min. The surgeons were asked to hold off manipulation. Blood pressure was treated with initiation of nitroprusside (0.2-0.3 mcg/kg/min) along with boluses of nitroglycerine and esmolol (after heart rate had recovered). Resection could be continued with adequate control of hemodynamic parameters. After conclusion of the thoracic part, the right lung was re-inflated and the patient was placed in supine position. The double-lumen endotracheal tube was exchanged to a single-lumen cuffed 5.5 endotracheal tube. Direct laryngoscopy again yielded a grade 1 view. Prior to surgical draping, the urology team attempted to empty the patient's bladder with a Foley catheter. During bladder catheterization, the patient again experienced hypertension (systolic blood pressure increase from 80 mmHg to 130 mmHg) with associated reflex bradycardia (heart rate decrease from 60/min to 30/min). Hemodynamics again normalized with cessation of the catheterization attempt which was resumed after initiation of nitroprusside and blood

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pressure control with nitroglycerine boluses. The urology team proceeded with cystoscopy, partial cystectomy and removal of the bladder mass.
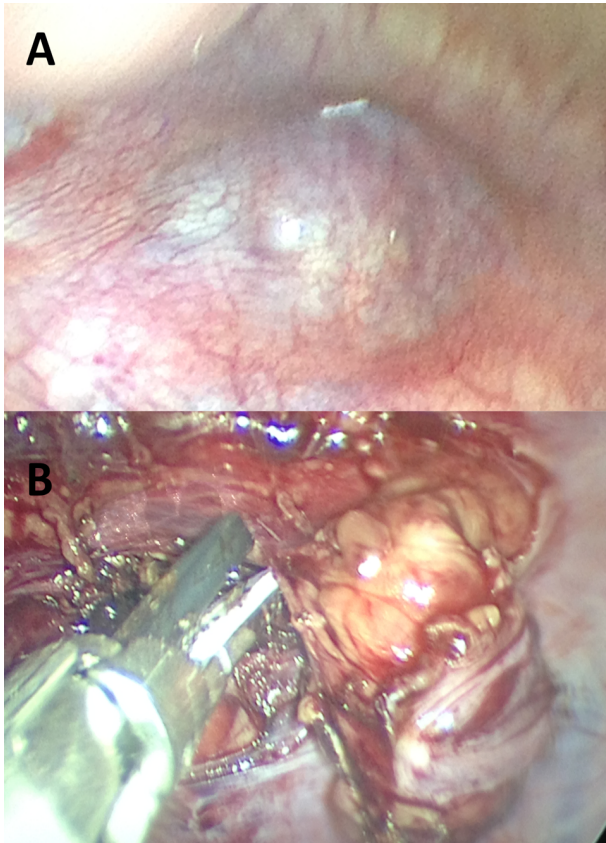

Figure 2 (a-b). Thoracoscopic resection of the paraspinal paraganglioma at the T10 level. A) View after lung deflation and introduction of the thoracoscope. B) Thoracoscopic view during paraganglioma resection.

During this part of the procedure, the patient again experienced milder forms of hemodynamic perturbations that could be controlled with nitroprusside and nitroglycerine. At the end of the procedure, bilateral transversus abdominis plane blocks and a right-sided paravertebral block were placed under ultrasound-guidance. Peripheral nerve catheters were left in place in all three block locations for postoperative pain control. Initial bolus dose consisted of 29 cc ropivacaine 0.2% distributed over the three block locations. The patient emerged from general anesthesia and was extubated in the operating room. Nitroprusside infusion was discontinued prior to extubation. He remained hemodynamically stable and was transported to the intensive care unit for postopera-

tive monitoring. Blood loss for the procedure was estimated to be 20 cc. The patient received a total of 1470 cc of crystalloids and made 280 cc of urine.

His postoperative course was uneventful. Pain control was reported to be good with a combination of local anesthetics via regional catheters, intravenous acetaminophen, ketorolac, morphine and oxycodone. Bladder spasms were treated with diazepam and oxybutynin. He was transferred to the floor on postoperative day 2 and discharged home on postoperative day 4. Histologic evaluation of the resected masses showed both of them to be paragangliomas. The bladder paraganglioma was completely resected. In contrast, the resected paraganglioma at the thoracic spine level was found to have positive margins. Given the attachment of the mass to the large sympathetic chain nerve the oncology care team decided to institute postoperative surveillance.

Postoperative follow-up for the first year was scheduled to include magnetic resonance imaging of the thorax (every three months), bladder ultrasound, whole-body magnetic resonance imaging and blood catecholamine levels (every three months). During the first three-month follow-up, the patient was doing very well. Laboratory studies including chromogranin A, plasma metanephrines and catecholamine levels were within normal limits. Bladder ultrasound and thoracic spine MRI were negative for new masses or tumor recurrence.

Discussion and conclusion

Pheochromocytomas and paragangliomas are rare neuroendocrine tumors in childhood with estimated incidence rates of 0.3 per million per year or less.[5] In the middle of the previous century, surgical approaches to resection of those tumors have been associated with perioperative mortality rates up to 50%. Those rates showed a slight decrease to 20-45% in reports from 1954 and 1967. The adult literature lists substantial intraoperative hemodynamic perturbations as causes for events such as myocardial ischemia, left ventricular failure, malignant arrhythmias and strokes. In the postope-

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rative period, removal of the catecholamine source may lead to prolonged postoperative hypotension and shock. The contemporary literature, however, shows significant improvements in outcomes. Plouin et al.[6] performed a retrospective review of 147 patients who underwent pheochromocytoma resection at a single institution between 1975 and 1997 and reported a 30-day mortality and morbidity (nonfatal cardiovascular events, thromboembolism, resection of a neighboring organ, further surgery, any infectious or incision problem extending hospitalization beyond ten days) rate of 2.4% and 23.6%, respectively. Kinney et al.[7] performed a similar retrospective analysis of 143 patients undergoing pheochromocytoma or paraganglioma resection at a single institution between 1983 and 1996. Within 30 days of the procedure, there were no perioperative deaths, myocardial infarctions, or cerebrovascular events. Intraoperative events (acidosis, sustained hypertension, sustained hypotension) occurred in 41 patients (28.7%) while postoperative events (pulmonary embolism, renal dysfunction, biliary dysfunction, prolonged endotracheal intubation, systemic sepsis) were observed in 9 patients (6.3%).

Nevertheless, functional paragangliomas/ pheochromocytomas present unique challenges for the anesthesiologist. As shown by a number of case reports, hemodynamic instabilities during surgery, especially in patients with previously undiagnosed neuroendocrine tumors, require close monitoring and aggressive intervention.[8] The amount of secreted catecholamines can change over the course of the procedure due to direct tumor manipulation, compression from pneumoperitoneum/ pneumomthorax in the setting of laparoscopy/ thoracoscopy and sympathetic stimulation from pain or laryngoscopy. Conversely, after successful resection of the tumor, refractory hypotension may ensure as the catecholamine stores are removed and the preoperatively established α-blockade becomes unopposed. Current recommendations for management of patients presenting for resec-

tion of a pheochromocytoma include: a) preoperative establishment of α-blockade (with the goal of achieving orthostatic hypotension); b) fluid administration; c) preoperative anxiolysis; d) close intraoperative hemodynamic monitoring; e) establishment of central venous access for administration of vasoactive medications; f) use of vasoactive medications to treat perioperative hemodynamic instability; and g) maintaining adequate anesthetic depth for stimulating parts of the procedure such as laryngoscopy and incision.[9] Fewer articles specifically focus on functional paragangliomas, but given the same underlying pathology and pathophysiology, similar anesthetic considerations apply.

While the decrease in morbidity and mortality over time is often attributed to preoperative establishment of α-blockade combined with fluid administration, some authors question whether this reduction is in fact due to a combination of factors including improvements in surgical techniques, intraoperative monitoring, anesthetic agents and postoperative care. Lentschener et al.[10] highlight that the critical period in management of functional neuroendocrine tumors is the immediate intra- and postoperative period in which blood pressure instabilities should be aggressively managed with careful surgical handling of specimens, limitation of intraabdominal/ intrathoracic pressure, muscle relaxation, adequate anesthetic depth and fast-acting vasoactive agents. From the preoperative evaluation in our presented case, it was apparent that at least one of the paragangliomas was functional. Secretion of norepinephrine upon stimulation of the thoracic and bladder mass was consistent with the hemodynamic response (α-agonism leading to vasoconstriction and hypertension followed by reflex bradycardia).

In conclusion, we describe the perioperative management of a child diagnosed with a *SDHB* germline mutation presenting with synchronous functional paragangliomas located in the thorax and pelvis. Our case highlights the importance of being prepared for intraope-

rative hemodynamic instabilities, even in patients who preoperatively do not exhibit overt signs and symptoms of chronic or paroxysmal hypertension. Manipulation of neuroendocrine tumors of the bladder, even as simple as bladder catheterization, should be performed in a setting that allows rapid diagnosis and treatment of a hypertensive crisis. During a literature review, we encountered multiple reports of synchronous non-functional paragangliomas in the head and neck region. We also found case reports of synchronous, non-functional paragangliomas in the head/neck region and thorax as well as in the retroperitoneum and bladder. To our knowledge, this is the first report of a successful anesthetic for resection of synchronous, functional paragangliomas located in thorax and pelvis in a patient with a *SDHB* germline mutation.

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