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CASE REPORTS/CASE SERIES

Case series: anesthetic management of patients with spinal and bulbar muscular atrophy (Kennedy's disease)

Présentation de cas: prise en charge anesthésique de patients souffrant d'atrophie musculaire spinale et bulbaire (maladie de Kennedy)

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Abstract

Purpose *Kennedy's disease (KD) is a rare, X-linked recessive, neurodegenerative disorder of lower motor neurons characterized by progressive proximal limb and bulbar muscular atrophy with spontaneous laryngospasm, which may present an anesthetic risk. We undertook a computerized search of the Mayo Clinic medical records database between January 1996 and May 2008 for patients with KD undergoing general anesthesia. Medical records were reviewed for anesthetic techniques and perioperative complications.*

Clinical features *We identified six patients with KD, confirmed by DNA testing, who underwent 13 general anesthetics. Succinylcholine was used in two patients, and non-depolarizing neuromuscular blockers in seven cases, all without adverse effects. Although laryngospasm was not identified in any patient, one patient with advanced disease experienced postoperative glottic edema, worsening respiratory distress, bulbar dysfunction, requiring tracheostomy and prolonged ventilatory support. One patient experienced a pneumothorax.*

Conclusion *The potential for bulbar dysfunction and muscle weakness in patients with KD places them at risk for perioperative complications from anesthesia. Anesthesia providers should be cognizant of the different potential anesthetic risk factors in these patients.*

Résumé

Objectif *La maladie de Kennedy est un trouble rare récessif lié au genre et neurodégénératif des neurones moteurs inférieurs caractérisé par l'atrophie musculaire progressive des membres proximaux et des bulbes, provoquant des laryngospasmes spontanés, ce qui peut engendrer un risque lors de l'induction de l'anesthésie. Nous avons entrepris une recherche électronique de la base de données des dossiers médicaux de la clinique Mayo entre janvier 1996 et mai 2008 pour les patients souffrant de la maladie de Kennedy et subissant une anesthésie générale. Les dossiers médicaux ont été passés en revue afin d'identifier les techniques anesthésiques utilisées et les complications périopératoires.*

Éléments cliniques *Nous avons identifié six patients souffrant de la maladie de Kennedy, confirmée par un test ADN, qui ont subi 13 anesthésies générales. La succinylcholine a été utilisée chez deux patients, et les bloqueurs neuromusculaires non dépolarisants dans sept cas; aucun effet secondaire n'a été observé. Bien que le laryngospasme n'ait été identifié chez aucun patient, un patient souffrant d'un stade avancé de la maladie a manifesté un œdème glottique, une détresse respiratoire se détériorant, un dysfonctionnement bulbaire, et a nécessité*

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une trachéotomie et un soutien respiratoire prolongé. Un patient a manifesté un pneumothorax.

Conclusion *La possibilité de survenue d'un dysfonctionnement bulbaire et de faiblesse musculaire chez les patients souffrant de la maladie de Kennedy constitue un risque pour ces patients de subir des complications périopératoires liées à l'anesthésie. Les prestataires d'anesthésie devraient être au fait quant aux différents facteurs de risque anesthésique potentiels pour ces patients.*

Kennedy's disease (KD), or spinal and bulbar muscular atrophy, is a rare, X-linked recessive, neurodegenerative disorder of lower motor neurons characterized by progressive bulbar and appendicular muscular atrophy.[1–3] Kennedy's disease has several important features which should be of concern to the anesthesiologist. Spontaneous, but self-limited laryngospasm occurs with increased frequency in this patient population,[3,4] and it is unknown if these patients are at increased risk of laryngospasm with airway manipulation during anesthesia. These patients can be debilitated in later stages of the disease and may have profound bulbar dysfunction with a theoretical increase in the risk of aspiration.[1] Given motor neuron involvement in KD, the safety of muscle relaxants has not been established. Due to the relatively long lifespan of patients with KD, it is likely that they will require anesthesia for surgical procedures. Presently, there is only a single case report describing the anesthetic management of a patient with KD.[5] We describe the perioperative considerations and the anesthetic care and outcomes in a small series of patients with KD.

Methods

After obtaining Institutional Review Board approval from Mayo Clinic Rochester, Minnesota, we conducted a computerized search of our Diagnostic Medical Index database, queried for KD from January 1, 1996 to May 31, 2008. Only genetically confirmed cases of KD, by polymerase chain reaction-based assay (performed by Mayo Clinical Laboratories on all patients) were included.[6] Anesthetic records of KD patients who underwent general anesthesia were manually reviewed by one of the authors, (A.D.N.). Data were entered into standardized data collection form and all questionable entries were discussed with the senior author (T.N.W.). We reviewed demographics (age, gender, year of operation), anesthetic technique, hemodynamic variability (blood pressure and/or heart rate episodes above or below 30%, measured before anesthesia induction) and hemodynamic instability (need for pressor/chronotropic drugs), and intraoperative body temperature. The charts were also reviewed to identify postoperative respiratory complications, including laryngospasm, residual paralysis from muscle relaxants, and postoperative respiratory failure requiring tracheal re-intubation or the rescue use of non-invasive positive pressure ventilation.

Results

The initial database review yielded 30 patients with KD confirmed by DNA testing. Of the patients with confirmed KD, six patients had undergone a total of 13 general anesthetics. Surgery included orthopedic, abdominal, oral, thoracic, and otorhinolaryngeal (tracheostomy) operations. One patient underwent a magnetic resonance imaging scan under anesthesia. The mean age of the six patients at the time of the procedures was 59 ± 14 year, with a range from 31 to 77 year (Table 1), and their mean weight was 85.0 ± 14.8 kg.

The anesthetic technique for each case was determined by the supervising anesthesiologist, and all cases involved general anesthesia. Prior to induction, most patients received midazolam 2 mg *iv*, and all patients received fentanyl 1–2 μg kg^{-1} *iv*. Anesthesia was induced with either propofol (1–2 mg kg^{-1}) or thiopental (3–5 mg kg^{-1}). In two cases involving the same patient, induction drugs were administered following an awake fiberoptic endotracheal intubation. Each patient received a neuromuscular blocking agent at induction during at least one procedure, with two patients receiving succinylcholine. At Mayo Clinic, it is common practice, with use of muscle relaxants, for physicians to titrate the dose according to a muscle response delivered from a standard peripheral neuromuscular stimulator. Anesthesia was maintained with volatile anesthetics, and, in addition, one patient also received a propofol infusion. Nitrous oxide was used in five patients and in 10 of the 13 identified anesthetics. Intraoperative warming was achieved using a forced air warming blanket and/or increase in ambient temperature (no significant hypo- or hyperthermia was recorded). Analgesia was achieved with either fentanyl or oxymorphone, and vecuronium was used to maintain neuromuscular blockade in three cases. Reversal of neuromuscular blockade was documented in four cases with the use of neostigmine as an anticholinesterase inhibitor and glycopyrrolate for antimuscarinic activity. Another common practice at Mayo Clinic is to reverse neuromuscular blockade after the return of at least one twitch using a train-of-four response. The administration of a reversal agent after use of non-depolarizing muscle relaxants was not documented in two procedures. No episodes of

Table 1 Demographics and other characteristics of patients with Kennedy's disease undergoing general anesthesia

	Patient 1				Patient 2	Patient 3	
Date of birth	11/7/1935				2/11/1953	7/5/1926	
Surgical date	11/23/2001	11/25/2001	11/27/2001	11/30/2001	3/15/1995	6/17/2002	7/29/2003
Age at procedure	66	66	66	66	42	75	77
ASA status	3	3	3	3	2	3	3
Procedure	Fasciotomy, external fixation tibia	Debridement and closure fasciotomy wound	Debridement, closure leg wounds, ORIF tibia	Tracheostomy	Cervical laminectomy	MRI lumbar spine under anesthesia	Revision total knee arthroplasty
Intubation technique	DL	Fibreoptic	Fibreoptic	DL	DL	DL	DL
Neuromuscular blocker at induction	None	None	None	Succinylcholine 120 mg	Vecuronium 10 mg	Vecuronium 6 mg	Vecuronium 10 mg
Maintenance neuromuscular blocker	None	None	None	None	Vecuronium 12 mg	None	None
Maintenance Volatile	*Isoflurane*	*Isoflurane*	*Sevoflurane*	*Isoflurane*	*Isoflurane*	*Isoflurane*	*Isoflurane*
Reversal administered	No	No	No	No	Not charted	Yes, 5 mg neostigmine; additional 2 mg when dyspneic post extubation	Yes
Surgical time	66 min	36 min	165 min	32 min	150 min	30 min	187 min
Laryngospasm	No	No	No	No	No	No	No
Postoperative level of care	Floor	Floor	Floor	ICU	Floor	ICU	Floor
Postoperative complications	Difficulty swallowing, ENT exam showed pharyngeal edema, placed on corticosteroids	None	Severe respiratory distress POD #4, to ICU, tracheostomy performed 11/30	PE POD #4, eventually to ventilator unit, dismissed from hospital POD #63, deceased POD #78 (pneumonia)	None	Tension pneumothorax discovered postoperatively, chest tube placed, intubated to ICU overnight	None

	Patient 4		Patient 5	Patient 6		
Date of birth	2/22/1951		3/31/1926	8/1/1948		
Surgical date	12/7/2006	5/9/2008	8/3/2000	7/16/1980	10/23/1993	1/25/1999
Age at procedure	55	57	74	31	45	50
ASA Status	3	3	3	2	2E	2
Procedure	Lumbar laminectomy, discectomy	Laparoscopic cholecystectomy	Mediastinoscopy, left VATS, wedge resection, talc pleurodesis	Odontectomy	Appendectomy	Excision hand mass
Intubation technique	DL	DL	DL	Nasal	DL	DL

Table 1 continued

	Patient 4		Patient 5		Patient 6	
Neuromuscular blocker at induction	None	Atracurium 50 mg	Succinylcholine 80 mg	None	Vecuronium 4 mg	Mivacurium 20 mg
Maintenance neuromuscular blocker	None	None	Vecuronium 13 mg	None	Vecuronium 4 mg	None
Maintenance Volatile	*Isoflurane*	*Sevoflurane and propofol infusion*	*Isoflurane*	*Enflurane*	*Isoflurane*	*Sevoflurane*
Reversal administered	No	Yes	Not charted	No	Yes	No
Surgical time	183 min	114 min	218 min	20 min	115 min	75 min
Laryngospasm	No	No	No	No	No	No
Postoperative level of care	ICA	Floor	Floor	Floor	Floor	Floor
Postoperative complications	None	None	None	None	None	None

MRI magnetic resonance imaging, *VATS* video assisted thoracoscopic surgery, *DL* direct laryngoscopy, *ICU* intensive care unit, *ICA* intermediate care area, *PE* pulmonary embolism, *ENT* ear, nose, and throat, *POD* postoperative day, *ORIF* open reduction and internal fixation

laryngospasm were identified. Intraoperative hypotension requiring intervention occurred during five procedures and were resolved with phenylephrine 100 μg *iv* or ephedrine 5 mg *iv*.

Two major complications were noted in this series. The first involved a patient who underwent general anesthesia for a fasciotomy and external fixation of a tibial fracture. This patient was elderly and had major debility from his KD, with proximal muscle weakness and bulbar dysfunction. Postoperatively, he developed dysphagia. Fiberoptic examination revealed severe glottic edema, which was treated with a course of corticosteroids. Due to pharyngeal edema, the patient's trachea was left intubated (initially performed fiberoptically) for the two subsequent operations related to management of his tibial fracture. Following tracheal extubation, the patient developed severe respiratory distress 3 days after the last operation, which was attributed to worsening bulbar muscle strength and decreased ability to clear upper airway secretions. The symptoms were treated with racemic epinephrine and supplemental oxygen. Fiberoptic examination revealed a narrowed glottic opening with minimal vocal cord abduction. A tracheostomy was performed later that day. Four days following the tracheostomy, the patient developed a pulmonary embolus with concomitant respiratory failure that required prolonged ventilatory support, with eventual wean 29 days after the tracheostomy. The patient was discharged from the hospital 70 days after his initial surgery, but he was readmitted 7 days later with a new right lower lobe pneumonia. He refused further intervention, was discharged home with comfort care measures, and died 8 days later.

A second patient developed a tension pneumothorax following general anesthesia for an out-patient diagnostic magnetic resonance scan. He received vecuronium 6 mg *iv* for tracheal intubation, and at the conclusion of the case, reversal of residual neuromuscular block was achieved with neostigmine 5 mg *iv* and glycopyrrolate 1 mg *iv*. Following extubation, the patient was noted to be dyspneic with inability to maintain oxygen saturations greater than 90%. Additional neostigmine and glycopyrrolate did not improve the patient's clinical condition. Accordingly, the patient's trachea was re-intubated. A chest radiogram demonstrated a moderate right-sided pneumothorax, and a chest tube was inserted. The patient was monitored in the intensive care unit, and his trachea was extubated following resolution of the pneumothorax with no further complications noted.

Discussion

Kennedy's disease was named after the neurologist, Dr. William R. Kennedy, who first described the disorder in

1968.[2] The underlying inherited defect is enlargement of the CAG trinucleotide repeat region in the first exon of the androgen receptor gene on the X chromosome.[6] The estimated worldwide incidence of Kennedy's disease is approximately one case in 40,000 males.[6] Patients with KD have a normal life span, but develop progressive disability with increasing age.[7] The clinical manifestations usually begin in the fourth decade of life.[1,8] Early symptoms include hand tremor, muscle pain (often associated with increased creatine kinase levels), and premature muscle exhaustion. The loss of lower motor neurons supplying the bulbar musculature results in bulbar symptoms such as difficulty with articulation[8] Up to 47% of patients also experience laryngospasms that occur spontaneously during routine daily activities, but are fortunately self-limited.[3,4] Later motor symptoms include proximal extremity weakness (more severe than distal), muscle atrophy, and fasciculations (particularly of the lower face), which begin to manifest in the fifth decade of life.[1,8] Profound bulbar dysfunction occurs late in the disease process, and these patients are at risk for repeated aspiration.[8] The disease is also marked by androgen insensitivity, and male patients can develop gynecomastia and testicular atrophy and are less likely to develop alopecia.[2,9,10] Some features of the clinical presentation of KD resemble the early stages of amyotrophic lateral sclerosis (ALS), and the disorder is often misdiagnosed.[9,11] However, KD lacks upper motor neuron signs and has a slower progression than ALS. In contrast to ALS, where small motor neurons are not lost, all types of motor neurons (large, medium, and small) are lost in KD.

Given the weakness from progressive degeneration of motor neurons in KD, several potential anesthetic risk factors exist, including problems with acute onset of laryngospasm, hyperkalemia with use of succinylcholine, increased sensitivity to non-depolarizing muscle relaxants, and postoperative respiratory failure or aspiration. However, a MEDLINE search of the available literature from the past 40 years revealed only one case report of successful use of epidural anesthesia for internal urethrotomy,[5] and no reports of the use of general anesthesia. This series describes the anesthetic management and clinical outcomes in a small group of patients with KD. There was no evidence of autonomic instability, significant hemodynamic or temperature perturbations. Intraoperative ventilation and oxygenation were unremarkable in all cases, except for the patient who developed a spontaneous tension pneumothorax. This patient did not have a central line placed, and we do not have a mechanistic explanation to link this complication to KD.

A retrospective review showed that, despite liberal use of neuromuscular blocking drugs in this series, complications attributable to the use of muscle relaxants were not observed. Two patients received succinylcholine to facilitate tracheal intubation without incident. However, patients with severe lower motor neuron disease, with loss of motor function and atrophy are considered to have an increased risk of a hyperkalemic response to succinylcholine.[12,13] It is recommended that succinylcholine be avoided for patients with a similar disorder, such as ALS.[14] Accordingly, given the small number of patients in our case series, the potential risk for such complications from depolarizing paralytic agents cannot be estimated; therefore, the possibility should not be ignored. Residual weakness from the use of non-depolarizing muscle relaxants was also not observed in this series. The one occurrence of a patient requiring additional neostigmine probably represented empiric treatment for hypoventilation and hypoxia, which was eventually revealed to be secondary to a tension pneumothorax and not residual weakness. Regardless, patients with KD have decreased levels of acetylcholine and may theoretically have an increased sensitivity to non-depolarizing neuromuscular blockade and the potential for residual weakness following reversal from non-depolarizing neuromuscular blockade.

In our series there were no recorded incidents of laryngospasm. Although no patient in our study experienced aspiration during induction or emergence, the increased risk of this problem is obvious. Desflurane was not used in this series, but its propensity to being an airway irritant should be considered prior to its use in these patients. Rapid sequence induction or awake intubation may be preferable, particularly in patients who have severe bulbar symptoms or a known history of aspiration. In this regard, the patient who experienced postoperative glottic edema did have preoperative bulbar dysfunction. However, it is not clear how this edema could be mechanistically linked to his significant bulbar dysfunction or his KD, since glottic edema is not a known complication of KD. Nonetheless, the respiratory distress noted 4 days after a general anesthetic was likely due to his inability to handle secretions, given his bulbar muscle dysfunction as well as continued problems with edema of his glottis. Thus, the subsequent tracheostomy and prolonged mechanical ventilation with difficult wean are not surprising. Unfortunately, his eventual demise only highlights the risk of respiratory complications in this patient population.

One patient in our series underwent a general anesthetic for excision of a hand mass. In retrospect, a regional technique may have been a safer alternative. However, a review of the anesthetic record could not determine the reason for choosing a general anesthetic for that particular case. To avoid manipulation of the airway in KD patients, it may be prudent to employ a regional anesthetic whenever possible.

Since KD is a very rare disorder, it is impossible to conduct large-scale studies to assess the safety of general

anesthesia in this group. Thus, we must rely on experience gained from reports of either individual cases or case series. In this small series, the patients safely underwent general anesthesia. However, the anesthesia provider should be vigilant, given the bulbar dysfunction and the possibility of laryngospasm. Although no complications from the use of neuromuscular blockade were observed in this small series, these patients may still have an increased sensitivity to muscle relaxants. These agents should be used judiciously and with close monitoring of clinical effects.

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Conflicts of interest None declared.

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