Anesthetic Management of Costello Syndrome: A Case Report

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Costello syndrome is a rare genetic disorder with an estimated 300 medical cases worldwide. Typical features that characterize this syndrome include short stature, macrocephaly, developmental delay, loose skin folds, distinctive coarse facial features, and multiorgan system anomalies. The following case report discusses the anesthetic management for a 3-year-old boy undergoing general anesthesia for a scheduled dental restoration, hydrocelectomy, inguinal hernia repair, and bilateral myringotomy with placement of pressure equalization tubes. A scarcity of literature for the anesthetic management of Costello syndrome (also known as faciocutaneoskeletal syndrome) exists. Utilizing an overview of the pertinent literature, clinical practice recommendations are suggested for the anesthetic implications of managing a pediatric patient with this rare syndrome.

Keywords: Anesthesia, Costello syndrome, faciocutaneoskeletal syndrome, rare genetic disorder.

Costello syndrome is a rare genetic disorder with an estimated 300 medical cases worldwide.[1-3] According to the National Institutes of Health, the prevalence ranges from 1 in 300,000 to 1 in 1.25 million people.[2] This condition, also known as faciocutaneoskeletal syndrome, affects many body systems. Typical features such as rare stature, megalocephaly, developmental delay, loose skin folds, distinctive coarse facial features, and multiorgan system anomalies characterize this syndrome.[3] At times, in infants and young children it may be difficult to distinguish Costello syndrome from cardiofaciocutaneous syndrome or Noonan syndrome.[1] Costello syndrome was first identified in New Zealand when a pediatrician noticed a striking similarity in the features between 2 unrelated children, including similar facial stigmata, nasal papillomas, and developmental delays.[4] Twenty years after the discovery of this disorder, now bearing his name, Dr Jack Costello contributed additional clinical observations that he noted in adult features of Costello syndrome.[5]

The paucity of literature addressing the anesthetic management of Costello syndrome has compelled the author to present an uneventful case of a 3-year old with Costello syndrome who required general anesthesia for dental restoration, hydrocelectomy, inguinal hernia repair, and bilateral myringotomy with placement of pressure equalization tubes. The discussion suggests practice recommendations for the anesthetic implications of managing a patient with this rare syndrome.

Case Summary

A 3-year old, 22-kg boy accompanied by his parents, presented to the preoperative holding area for a scheduled dental restoration, hydrocelectomy, inguinal hernia repair, and bilateral myringotomy with placement of pressure equalization tubes. The patient had no known allergies to foods, medications, or latex products. The birth history included a normal full-term birth via vaginal delivery, with a diagnosis of Costello syndrome made shortly after birth. The past medical history was notable for resolved mild gastroesophageal reflux disease (GERD) and annual visits to a cardiologist. Current medical conditions included a right hydrocele, right inguinal hernia, dental caries, and chronic otitis media. No surgical history existed. The parents denied any family history of life-threatening anesthetic complications. No preoperative laboratory work had been done. The patient had had nothing by mouth for 10 hours. He was not taking any medications. His medical history included no epistaxis or choanal atresia. A written cardiology consultation report indicated that the patient had no evidence of cardiac abnormalities and that findings of both a recent transthoracic echocardiogram and electrocardiogram (ECG) were normal.

On physical examination of the patient, the following characteristic features were noted: down-slanted palpebral folds, epicanthal folds, low nasal bridge, megalocephaly, curly hair, short and stocky stature, short neck, pigmented and thickened skin with noticeable papillomas on exposed areas of skin, gingival hyperplasia, and broad, full lips. On auscultation, bilateral lung fields were clear, and the patient's resting heart rate and rhythm were regular. Preoperative vital signs were normal. The interview process revealed a very warm, active, and cooperative child with articulate speech and above-average vocabulary for his age.

After an informed written consent was obtained, an anesthetic management plan was implemented. No midazolam was administered preoperatively given the gregarious personality of the patient. One parent was

Author	Year	Surgical procedure	Anesthetic outcome	Age
Dearlove and Harper[8]	1997	Exploratory laparotomy	Transient desaturation; Otherwise uneventful	2 y, 6 m
Benni et al[9]	2002	Left orchiopexy	Transient desaturation; Otherwise uneventful	1 y, 8 m
Katcher et al[10]	2003	Rigid bronchoscopy, direct laryngoscopy, tonsillectomy and bilateral pressure equalization tubes	Uneventful	2 y, 4 m
Shukry et al[11]	2008	Central line placement	Hypoxia, followed by cardiac arrest	4 m
Tsutsui et al[12]	2009	Scoliosis repair	Complicated by massive intraoperative hemorrhage	10 y

Table 1. Literature Review of the Anesthetic Outcomes of Patients with Costello Syndrome

present for the induction of anesthesia.

After the patient's entry into the operating room, standard American Society of Anesthesiologists (ASA) monitors were placed.[6] An inhalation induction with the patient in the supine position proceeded with a 30/70 mixture of oxygen and nitrous oxide and a slow, steady introduction of sevoflurane in 2% increments. After the patient lost consciousness, the circulating nurse escorted the parent out of the operating room. An oral airway was placed, accompanied by 10 cm H_2O of continuous positive airway pressure to keep the airway patent and to relieve obstruction. Following placement of a 22-gauge intravenous catheter (Jelco, Smiths Medical) in the left hand, nitrous oxide therapy was discontinued and 100% oxygen was administered in an 8% sevoflurane mixture. Bag-mask ventilation was easily managed. In preparation for a nasal intubation, 0.5 mL of oxymetazoline was administered to each naris. After fentanyl (1 µg/kg) and propofol (2 mg/kg) were administered intravenously, the patient was successfully and nontraumatically intubated using a 4.5-mm cuffed nasal Ring-Adair-Ewlyn endotracheal (ET) tube that was inserted through the right naris. Proper ET tube placement was confirmed, and the tube was secured with tape. A noted cuff leak of 22 cm H_2O required no inflations of the ET tube cuff. The patient was placed on a pressure support ventilation mode and vital signs remained stable throughout induction.[7]

Once the operating table was turned 90 degrees, the dental rehabilitation procedure began. Afterward, the bilateral myringotomy and tubes placement began, followed by a right hydrocelectomy and a right inguinal hernia repair. Intraoperatively, the anesthetic depth was maintained with sevoflurane in a 50% air-oxygen mixture. Morphine (0.1 mg/kg) and ondansetron (0.1 mg/kg) was administered intravenously during the latter half of hydrocele repair.

The procedures were all accomplished without incident. The total estimated surgical blood loss was less than 25 mL. Sevoflurane therapy was discontinued, 100% oxygen was administered, and once the patient was awake and breathing spontaneously, his mouth was suctioned and the trachea was extubated. The patient was transported to the postanesthetic care unit, with supplemental blow-by oxygen via a Jackson-Rees circuit. He arrived somnolent, with an oxygen saturation of 99%. The remaining postoperative stay was without incident, and the patient was discharged home 4 hours later.

Discussion

An Ovid MEDLINE (database 1946-2012) search was conducted using the following search terms: *Costello syndrome, faciocutaneoskeletal syndrome, anesthesia,* and *airway management*. Fewer than 189 results were generated; however, 5 case reports were relevant to the anesthetic implications of managing a patient with Costello syndrome[8-12] (Table 1).

Three of 5 case reports listed in Table 1 indicate respiratory events as a common theme.[8,9,11] Although cardiac arrest is preceded by hypoxia in one case report, succinylcholine may have been implicated as the root cause.[11]

Costello syndrome is a genetic disorder caused by a mutation in the *HRAS* gene, resulting in a functional deficiency and defect in the production of elastin-binding protein, and leading to multiple-organ system anomalies, most notably in ectodermal tissues.[10,13,14] The classic presentation of this genetic mutation initially manifests as polyhydramnios and increased weight at birth followed by a postnatal failure to thrive, slow growth pattern, and poor feeding; developmental delay or mental retardation; papillomas, most frequently appearing in perioral, nasal, and anal regions; hypertrophic cardiomyopathy, cardiac valve disease and dysrhythmia; megalocephaly, macroglossia, and tonsillar and supraglottic hypertrophy; coarse facial features, including a depressed nasal bridge, epicanthal folds, and thick lips; and loose, redundant skin, especially on the neck, palms, and soles.[6,10,13-15] Other system manifestations of Costello syndrome are usually present.[15-18] Table 2 lists principal manifestations of Costello syndrome in 7 main categories.

Distinguishing Costello syndrome from Noonan syn-

System category	Manifestations[10,15-18]
Craniofacial features	Relative macrocephaly, coarse facial appearance, down-slanting palpebral fissures, epicanthic folds, strabismus, low-set ears, macrostomia with thick lips, high arched palate, gingival hypertrophy, and depressed nasal bridge
Respiratory problems	Hypertrophied tonsillar and supraglottic tissues; laryngeal papillomata, and choanal atresia
Cardiac anomalies	Hypertrophic cardiomyopathy, valvular thickening, prolapsed mitral valve, atrial tachycardia, and other rhythm abnormalities
Ectodermal anomalies	Sparse, fine, curly hair; redundant skin on neck, hands and feet; deep palmar and plantar creases; papillomata, and hyperpigmentation
Musculoskeletal abnormalities	Short neck, hyper-extensible joints due to joint laxity and hypotonia, kyphoscoliosis, pectus excavatum, tight Achilles tendon, upper and lower limb positional defects, and osteoporosis
Growth, development and nutrition	Birth weight greater than 50th percentile; followed by postnatal growth deficiency and weight loss due to progressive failure to thrive and feeding difficulties; GERD; mild-to-moderate mental retardation; sociable; hypoglycemia is a common feature in neonates
Miscellaneous	Cryptorchidism, at high risk for malignant tumors, especially rhabdomyosarcoma and neuroblastoma

Table 2. Manifestations of Costello Syndrome in System Categories

drome and other faciocutaneous syndromes in infancy is diagnostically challenging.[1,16] Hallmark features such as joint laxity, papillomas, redundant skin of the palms and soles in the setting of feeding difficulties, and failure to thrive usually support the clinical diagnosis.[1,15,16] Molecular genetic testing for the *HRAS* gene mutation is the diagnostic gold standard for Costello syndrome.[10] Proposed diagnostic guidelines have been published.[19] There is no cure for Costello syndrome.[20]

To put the statistical odds in perspective for the anesthesia provider, the rarity of encountering a patient with Costello syndrome is that one has better odds of being struck by lightning—at least 30 times in a lifetime[21]—or of being attacked by a shark at least once.[22] To compound the matter, the scarcity of literature on anesthetic management of these patients is at a premium, often leaving anesthesia providers with a knowledge-based deficit in rendering the safest care possible, tailored specifically for this population.

Although the perioperative course for the 3-year old boy in this case report was uneventful, many chance opportunities could have altered the clinical outcome despite the best intentions. The craniofacial and hypopharyngeal anomalies seen in Costello syndrome have the potential to hinder bag-mask ventilation, make tracheal intubation difficult or near impossible, and make placement of a laryngeal mask airway (LMA) dubious, depending on the degree of anatomical airway distortion. The anesthesia provider's investigatory skills during the preanesthetic interview will identify salient characteristics of Costello syndrome that may complicate anesthetic management. Cardiac anomalies, including hypertrophic cardiomyopathy, nonprogressive pulmonary stenosis, and multifocal atrial tachycardia, are an important and common feature of Costello syndrome.[23,24] This patient had no evidence of cardiac abnormalities at the time of surgery, but cardiac risks among patients with Costello syndrome still abound, making anesthetic implications even riskier. In a cohort with Costello syndrome, 60% of patients revealed cardiac abnormalities in varying degrees of ventricular septal defects, pulmonary stenosis, mitral valve prolapse, and patent ductus arteriosus.[25] In the same cohort, 18% of patients were reported as having some type of tachyarrhythmia, and 3 patients experienced sudden cardiac death.[10,25] A preoperative cardiology consultation for surgical clearance, a recent ECG, and an echocardiogram are highly advisable before the patient undergoes anesthesia and surgical stress.

Notable characteristics of Costello syndrome that may have an impact on airway management include a short neck, microcephaly, glossoptosis, macroglossia, hypertrophied tonsils, laryngeal malformation, and nasal and laryngeal papillomas.[5,23,26-29] In one study of obstructive sleep apnea, as evidenced by polysomnography, an abnormally high apnea-hypopnea index was present in 7 of 10 patients with Costello syndrome.[30] In the present case, a preinduction functional assessment of the patient's airway revealed many considerations for anticipated problems during anesthetic management. One predictive factor of difficult bag-mask ventilation related to the syndrome includes a history of obstructive sleep apnea, even in the absence of obesity and hypertrophied tonsils.[30] A high index of suspicion for upper airway papillomas is warranted, as their presence would have an impact on effective ventilatory management. A few papillomas were on exposed areas of the patient's arms. No skin lesions were observed in the perioral cavity during preoperative inspection. Other predictive factors associated with difficult bag-mask ventilation such as disruption of lower facial continuity, pulmonary diseases associated with increased airway resistance or decreased pulmonary compliance, obesity, or a misshapen head are not typical features of Costello syndrome; its presence would compound airway challenges.[23,31,32] Other func-

Perioperative phase	Anesthetic management recommendations[8-12,35]
Pre-operative	Schedule an anesthetic consultation prior to the scheduled day of surgery.
	Perform a comprehensive history and physical exam.
	Inquire about other previous diagnostic tests such as CT scan reports, chest x-ray, electroencephalogram (EEG), etc.
	Verify therapeutic levels of anti-seizure medications prior to induction.
	Investigate prior reactions to anesthetics, if applicable.
	Secure pre-operative cardiac diagnostic results, including ECG and recent echocardiogram report.
	Measure serum glucose and seek consultation, depending on endocrine involvement.
	Review pre-op intake of medication, especially for GERD and cardiac anomalies.
	Consider placing a pre-induction peripheral intravenous catheter.
	Pretreatment with an H_2-receptor antagonist and/or proton-pump inhibitor for severe GERD.
	Consider administering an oral midazolam to ease separation of the patient from the parent or allow parental presence during induction.
	Prepare back-up airway equipment such as LMAs and fiber optic airway management devices, including bronchoscope.
	Recruit assistance from other anesthesia providers.
	Have a variety of facemask sizes available.
Intra-operative	Use a 5-lead ECG monitoring system and recording a pre-induction rhythm strip.
	Monitor core temperature closely.
	Empty the stomach post-induction to further diminish the risk of silent aspiration.
	Use a cuffed ETT and have various tracheal tubes and LMAs, sized above and below readily available.
	When possible, consider the least intrusive airway management (ie, spontaneously breathing via face mask > spontaneously breathing with LMA > tracheal intubation.)
	Consider avoiding muscle relaxation, if possible.
	Do not administer muscle relaxation until mask ventilation has been demonstrated.
	If muscle relaxation is indicated, avoid succinylcholine if possible; otherwise co-administer with atropine.
	Reduce the dose and frequency of nondepolarizing muscle relaxation and monitor train-of-four closely.
	Check serum glucose during a long surgical procedure, especially in neonates.
	Carefully titrate opioids due to the respiratory depressant effects.
Post-operative	Extubate patient wide-awake.
	Closely monitor for upper airway obstruction and diminished respiratory reserve, especially after procedures on ear, nose, throat, head, and neck.
	Patient should be monitored and observed for a prolonged period beyond the typical discharge period for same-day surgery.
	Consider admitting the patient overnight.

Table 3. Anesthesia Practice Recommendations for Managing Costello Syndrome
Abbreviations: ECG, electrocardiogram; LMA, laryngeal mask airway.

tional assessment components revealed no history of obstructive sleep apnea, pulmonary disease, chronic upper respiratory tract infections, air hunger (Kussmaul respiration), or inability to lie supine. Airway adjuncts (oral airway, ProSeal LMA, Unique LMA) for anticipated difficult mask ventilation were available during induction.

The constellation of anatomical features coupled with the propensity for upper respiratory obstruction predisposes the patient with Costello syndrome to an intrathoracic obstruction—hence, this author's decision to proceed initially with an inhalation induction to maintain the patient's spontaneous respirations until securing the airway.[30,33] Inhalation induction maintains spontaneous ventilations better than use of intravenous propofol.[34] The decision to implement an inhalation induction with this patient superseded the necessity for a rapid-sequence induction afforded by the patient's history of mild GERD, not requiring pharmaceutical treatment. A rapid-sequence induction is generally preferable to inhalation induction in a patient presenting with severe GERD due to the risk of aspiration pneumonitis, but the dubious nature of this syndrome's airway features mitigate that priority.[34]

Sensitive predictors of difficult laryngoscopy and intubation specific to Costello syndrome are a short neck, possible creating difficulty bringing the glottis into view; a high arched palate, making passage of an ET tube a problem; and congenital laryngeal distortion.[31,32] Nasal papillomas, if present in this case, would have impeded nasal intubation. The presence of megalocephaly did affect initial positioning for intubation but was easily corrected with placement of a rolled towel to elevate the shoulders. Macroglossia was not present, and the patient's large oral aperture with unrestricted mouth opening was predicted to facilitate laryngoscopy. Preoperative history and results of the patient's physical examination disclosed no muffled or hoarse voice, no difficulty swallowing, and no secretions or stridor, all of which herald a difficult airway.[31,32] Alternative airway adjuncts available as backup for difficult laryngoscopy and intubation included a fiberoptic endoscope, a video laryngoscope, a gum-elastic bougie, and various LMA brands and sizes. The absence of pulmonary disease, cervical spine disease, or a history of a disrupted airway combined with this patient's unrestricted mouth made the LMA a viable backup airway adjunct.[31,32] An ear-nose-throat surgeon was on standby in the immediate area during induction.

Katcher et al[10] assert that mental retardation is a universal finding of Costello syndrome. However, the patient in this case showed no signs of mental retardation. It would be prudent to consider oral midazolam to facilitate parental separation.[10] A low threshold for allowing parental presence during induction is recommended. Muscle relaxants were not administered in this patient, but one case report suggests decreasing the dosing frequency in the setting of hypotonia because of the prolonged effects observed.[10] Other case reports uncover conflicting results after succinylcholine administration ranging from no adverse effects to perioperative hyperthermia and cardiac arrest.[8,10,11] There are published reports of cases with endocrine involvement.[26,27] Anesthetic implications would dictate further preoperative investigation and checking a perioperative glucose level. Isolated cases of Costello syndrome coupled with other disorders, such as glycogen storage disease, neurofibromatosis, and congenital absence of the portal vein have been reported.[12,35-37] Overall, the outlook on anesthetic clinical outcomes for the pediatric patient with Costello syndrome is positive when the inherent risk factors associated with the syndrome are adequately anticipated and promptly addressed.[8-10]

Conclusion

As researchers continue to investigate the enigmatic aspects of Costello syndrome, anesthesia providers are advised to approach perioperative management of this population cautiously and conservatively. Table 3 summarizes a constellation of practice recommendations gathered from a paucity of case reports. The anesthesia community is encouraged to contribute to the body of growing evidence after a rare encounter with a patient who has Costello syndrome.

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