

## Multiple Anesthetics for Proton-Radiotherapy in a Child with Costello Syndrome

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### Abstract

Costello syndrome (CS) is a rare genetic disorder caused by heterozygous germline Harvey rat sarcoma viral oncogene homolog (HRAS) gene mutations, and characterized by multi-system organ abnormalities. Associated craniofacial, cardiac, neurologic and musculoskeletal abnormalities may pose specific anesthetic challenges. Careful pre-anesthetic evaluation and planning is therefore essential to ensuring the safe delivery of care. In this case report, total intravenous anesthesia (TIVA) with propofol and spontaneous ventilation was successfully used to facilitate 28 proton-radiotherapy treatments in a child with Costello syndrome. TIVA with LMA was also successfully used during anesthesia for MRI of the pelvis.

### Keywords

Costello syndrome; Anesthesia; Radiotherapy; Cancer

### Introduction

Costello syndrome (CS) is a rare genetic disorder caused by heterozygous germline HRAS gene mutations, and characterized by multi-system organ abnormalities [1]. While previously diagnosed on the basis of clinical findings, recent identification of HRAS gene mutations as the underlying cause has enabled the differential and specific diagnosis of CS [2]. Since the discovery of the causative genes, approximately 150 new cases of CS have been reported [3]. Current reported estimates of the prevalence of CS range from 1 in 300 000 to 1 in 1.25 million people [4].

Characteristic features of CS include relative macrocephaly, a large mouth, large lips, a short neck, and low set ears [5]. Associated hypertrophic oro-pharyngeal tissue, choanal atresia, a high arched palate and laryngeal papillomata may also be present [6]. Cardiac, musculoskeletal, and central nervous system abnormalities have also been reported [7-9]. Patients with CS have also been shown to have an increased predisposition to certain malignant tumors including rhabdomyosarcomas, neuroblastomas, and transitional cell carcinomas of the bladder [10]. Due to the associated multisystem organ abnormalities, patients with CS may require diagnostic and therapeutic procedures under anesthesia. However, the

craniofacial and multisystem organ abnormalities may pose specific anesthetic challenges.

We present and discuss the anesthetic management of a 17 month old child with CS, who was diagnosed with a seminal vesicle spindle cell embryonal rhabdomyosarcoma, and required a total of 30 anesthetics for the purposes of diagnostic imaging and proton-radiotherapy treatment.

## Case Presentation

A 17 month old, 10 kg child with CS and a seminal vesicle spindle cell embryonal rhabdomyosarcoma presented for anesthetic management to facilitate a course of proton-radiotherapy treatments to the pelvis. Other medical history was significant for laryngomalacia, for which the child had undergone a supraglottoplasty, a patent ductus arteriosus (PDA), gastroesophageal reflux disease (GERD), a tethered cord at L4, and a seizure disorder. Seizures activity was rare and considered well controlled with divalproex and levetiracetam. GERD was considered mild, and well controlled with lansoprazole. The child was also 12 weeks into a chemotherapy regimen which included vincristine, dactinomycin, cyclophosphamide and irinotecan. There were no known drug allergies, and vaccinations were up to date. Prior anesthetics at an outside institution had been associated with cases of post-extubation croup. Although there was no official diagnosis of obstructive sleep apnea, the family reported that the child was unable to lie on his back because of difficulty breathing. The child was followed by an outside network of pediatric specialists including a cardiologist, an endocrinologist, gastroenterologist, neurologist, otolaryngologist and a geneticist. Physical examination was significant for characteristic craniofacial and musculoskeletal features of CS including relative macrocephaly, flattened nasal bridge, a short neck, low set ears, and positional deformities of the upper and lower extremities. Vital signs were appropriate for age, and laboratory values were unremarkable. The patient had a preexisting central venous line.

An initial computer tomography scan, followed by a total of 28 proton-radiotherapy sessions were scheduled to begin every Monday through Friday, with a break over the weekends. The patient was scheduled to be treated early in the morning in order to avoid prolonged fasting periods, and intake of fluids was encouraged up to 2 hours before the procedure. An anesthetic plan was formulated, and involved total intravenous anesthesia (TIVA) with propofol, and supplemental oxygen delivery by nasal cannula. The typical daily anesthetic management was as follows: after placement of standard monitors, a slow intravenous induction with incremental boluses of propofol was performed with the child in a seated position. After loss of consciousness, the child was gradually placed supine, and a continuous infusion of propofol was initiated. There was no significant airway obstruction after positioning supine, and no airway adjuncts were required. Adequate hydration was ensured with 20 ml/kg (200 ml) of 0.9 % saline infusion over the duration of treatment. Ondansetron was routinely administered for prophylaxis against nausea and vomiting. Treatment sessions lasted anywhere from 24 to 53 minutes, for a total cumulative time of 997 minutes under anesthesia. Daily induction doses of propofol ranged from 20 to 60 mg, while maintenance doses ranged from 250-275 mcg/kg/min. With the exception of a single day when the child was slow to awaken, and another occasion when hypotension was noted upon induction, this anesthetic regimen was well tolerated.

After the 7<sup>th</sup> treatment, magnetic resonance imaging of the abdomen and pelvis was ordered to evaluate treatment response. The decision was made to utilize a laryngeal mask airway to

enable assisted and interrupted ventilation, which would facilitate better imaging during particular MRI sequences. For this anesthetic, a slow induction was performed with propofol (total of 50 mg), after which easy face-mask ventilation was established with the aid of an oral airway. A size 2 laryngeal mask airway (LMA) was placed without difficulty, and the child was maintained on a propofol infusion (300 mcg/kg/min) while spontaneously breathing. The anesthetic was uneventful, and the patient was discharged home after recovery. The weekend after the 16<sup>th</sup> anesthetic, the child was admitted to the hospital due to increased seizure activity. An electroencephalogram and laboratory results were unremarkable, therefore an MRI under anesthesia was ordered to rule out any intracranial pathology. TIVA with propofol and spontaneous ventilation was used in this instance. After a slow induction with incremental boluses of propofol (total of 110 mg), an infusion at 250 mcg/kg/min was used for maintenance. The anesthetic was again uneventful, and the patient was discharged from the recovery room to the ward in stable condition. The seizure activity was ultimately attributed to decreased serum levels of divalproex, and resolved after dosing was adjusted accordingly.

## Discussion

While a constellation of features have been described in patients with CS, no single feature is unique for CS, and not all of the described features may be present in a single patient. Additionally, the absence of a particular feature may not rule out the presence of others [11]. Furthermore, certain mutations of the HRAS gene, for example the p.G12C genotype, may be associated with more severe medical problems in the affected individual [12]. Multi-specialty care is often required for this group of patients. Therefore, the anesthetic management warrants a thorough pre-anesthetic evaluation to determine the presence and severity of other systemic manifestations.

Airway challenges remain a primary concern for anesthesiologists administering care for patients with CS. In our patient, a history of laryngomalacia with frequent episodes of postoperative croup was an indication of airway abnormalities. Daily intubation or laryngeal mask airway placement could pose a risk for laryngo-tracheal edema, which could have further complicated his treatment course. A decision was made to use a non-invasive method of oxygen and anesthetic delivery for the radiotherapy sessions. Although the single use of an LMA was uneventful in our patient, gastrointestinal manifestations of CS including severe gastro esophageal reflux disease (GERD) may preclude the safe use of an LMA [13]. Due to the history of airway obstruction during sleep, a gradual induction of anesthesia was carried out with the child in the sitting position. The child was gradually placed supine while maintaining spontaneous ventilation and avoiding complete airway obstruction with the 'chin lift' maneuver. Supine positioning was routinely accomplished in this manner with minor to no airway obstruction. After treatment, the child was placed in the recumbent position for recovery.

Certain features of CS including relative macrocephaly, a short nose, macroglossia, and hypertrophied oropharyngeal tissue may make mask ventilation challenging [14]. In our patient, an oropharyngeal airway was used to attain adequate mask ventilation prior to LMA placement. Other authors have also described the use of an oropharyngeal airway to aid in achieving adequate bag mask ventilation in patients with CS [4, 15]. During intubation, hypertrophic oropharyngeal tissue combined with copious oropharyngeal secretions may lead to difficulties in visualizing and/or identifying airway structures [16, 17]. In their case report on the anesthetic implications of Costello syndrome, Katcher et al.

described an intubation sequence where cricoid pressure was applied from the onset. Unlike the experiences of Dearlove and Benni, Katcher et al. had no difficulty with visualization of the vocal cords, or intubation [15]. Application of cricoid pressure from the onset should perhaps be considered in order to ease problems with visualization of the vocal cords. Due to the described potential difficulties with intubation, difficult airway equipment including oropharyngeal airways, LMAs of various sizes, and a fiberoptic bronchoscope should be available at the time of intubation.

Neurologic manifestations of CS may include seizures [5, 9]. In our patient, an increase in the frequency of seizure activity was attributed to a decrease in therapeutic serum levels of divalproex. The contribution of our anesthetic management to this decrease in serum levels of divalproex is unclear. The most frequently administered medication was propofol, which has been shown to inhibit the activity of the major human cytochrome P450 enzyme CYP2C9 (tolbutamide 4'-hydroxylation). The enzyme CYP2C9 is involved in the metabolism of divalproex, and a significant inhibition of the enzyme could have resulted in an increase in serum levels of the drug, not a decrease [18, 19]. Cerebellar abnormalities including Chiari type 1 malformations with associated syringomyelia have been reported in some patients with Costello syndrome [9]. Furthermore, a systematic review of brain and spinal cord MRI studies revealed posterior fossa crowding with tonsillar herniation in 96% of individuals with CS. This posterior fossa crowding was observed to progress in a majority of those with serial studies [20]. It may therefore be important to avoid excessive flexion or extension of the neck during airway manipulation of these patients. Hydrocephalus and a tethered cord are other neurologic manifestations of CS. For that reason, maintenance of normocapnia, and measures aimed at avoiding increases in intracranial pressure should also be considered.

Cardiovascular abnormalities including valvular pulmonary stenosis, hypertrophic cardiomyopathy (HCM), atrial tachycardia, and prolapsed mitral valve have been reported in 60-75% of patients with CS [21]. Multi-focal atrial tachycardia may worsen in about 25% of those with arrhythmias, and the rapid development of severe HCM has been reported in infants with CS [7]. Also, severe bradycardia, followed by cardiac arrest has been reported after the administration of succinylcholine in a patient with CS [22]. Therefore, it is essential that these patients are under the care of a cardiologist, and a preoperative cardiac evaluation including an electrocardiogram and echocardiogram may be beneficial [5]. Our patient had a PDA and was being followed by an outside cardiologist for surveillance of his cardiac status. There were no reports of cardiopulmonary compromise prior to the initiation of treatment. Although the majority of treatments were completed without hemodynamic complications, a brief episode of hypotension (systolic blood pressures in the 50s) was noted upon induction on a day where technical difficulty in the synchrotron resulted in delay of treatment by 2 hours. Normal vital signs were restored after intravenous fluid (IV) hydration, and the radiotherapy session was completed without further complications. It was presumed that the prolonged fasting time associated with the delay may have contributed to the observed hypotension. For this reason, the parents were instructed to check-in for IV hydration if delays occurred in the future, as the child appeared very sensitive to changes in volume status. No further treatment delays or hypotensive episodes were encountered during the remaining course of treatments.

Musculoskeletal abnormalities in the form of upper and lower limb positional defects, joint laxity, hypotonia, and kyphoscoliosis may be present in patients with CS [8]. In order to prevent subluxation of

joints, special attention was paid to the positioning of the extremities during anesthesia, and during transfer of the child from the treatment cradle to the stretcher.

## Conclusion

In summary, TIVA with propofol and spontaneous ventilation was successfully used to facilitate 28 proton-radiotherapy treatments in a child with Costello syndrome. An LMA with propofol TIVA was also successfully used during anesthesia for MRI of the pelvis.

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