ANESTHETIC MANAGEMENT IN A PATIENT WITH CORNELIA DE LANGE SYNDROME

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Introduction

Cornelia de Lange syndrome (CdLS), also known as Brachmann−de Lange syndrome, is a syndrome of multiple congenital anomalies of variable severity. This rare syndrome is genetically heterogeneous and sporadic, with an estimated prevalence of 1 in 10,000 to 30,000. First described by Cornelia de Lange as a diagnostic entity in 1933, Vrolik and Brachmann reported isolated cases in severely affected infants between 1849 and 1916. The syndrome is best characterized by distinctive facial appearance, prenatal and postnatal growth deficiency, psychomotor delay, and upper limb malformations. Although almost all organ systems can be affected, individuals with CdLS most notably display deficits in the development of neurosensory, craniofacial, musculoskeletal, cardiac and gastrointestinal systems. There is no known cure but the syndrome can be managed by treating associated clinical symptoms. Sixty six percent of CdLS individuals die before the first year of life[1]. Mortality occurs primarily from aspiration in infancy and from infection and bowel obstruction there after[1].

Pathogenesis

Several genes have been discovered in CdLS (NIPBL, SMC1A, SMC3), all of which are involved in sister chromatid cohesion. Cohesion proteins are involved in chromosome segregation, regulation of gene expression, DNA repair and maintenance of genome stability. Mutations in NIPBL on chromosome 5 account for~ 60% of CdLS cases, while mutations in SMC1A on the inactivated X chromosome, and SMC3 on chromosome 10 account for ~5%[2]. NIPBL and SMC3 mutations are both believed to have an autosomal dominant inheritance. SMC1A mutations are believed to have an X-linked dominant pattern of inheritance, however males and females are affected similarly. The genotype-phenotype correlation reveals that mutations in NIPBL result in more severe phenotypes than mutations in SMCA1 and SMC3 genes[2]. Moreover, the associated phenotype in NIPBL mutations increases in severity as the severity of the mutation increases. More severe mutations occur in NIPBL deletions or truncations, while milder forms of CdLS occur in patients with NIPBL missense mutations. SMCA1 and SMC3 gene mutations are predominantly missense and small in-frame deletions. The phenotype in patients with SMCA1 and SMC3 mutations is milder, consisting mainly of mild to moderate mental retardation, without associated severe growth retardation, limb or systemic involvement[3,4]. Although mutations in these genes are implicated in 65% of patients, the pathogenesis of most cases of CdLS is sporadic and dominant[2].

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Clinical Manifestations

CdLS is diagnosed based on clinical signs and symptoms (Table 1).

Table 1
Diagnostic Criteria for Cornelia de Lange Syndrome

Body category	No.	Main criteria	With	Secondary criteria
(1) Facial		Synophrys (arched, fine eyebrows)	and >3 of	Long eyelashes
				Short nose, anteverted nares
				Long, prominent philtrum
				Broad or depressed nasal bridge
				Small or square chin
				Thin lips, down-turned corners
				High palate
				Widely spaced or absent teeth
(2) Growth	>2 of	Weight below 5th centile for age		
		Height or length below 5th centile for age		
		OFC below 2nd centile for age		
(3) Development	>1 of	Developmental delays or mental retardation		
		Learning disabilitites		
(4) Behavior	>2 of	Attention deficit disorder ± hyperactivity		
		Obsessive-compulsive characteristics		
		Anxiety		
		Constant roaming		
		Aggression		
		Self-injurious behavior		
		Extreme shyness or withdrawal		
		Autistic-like features		
(5) Musculoskeletal		Reduction defects with absent forearms	alone	
	OR	Small hands and/or feet (below 3rd centile) or Oligodactyly	and >2 of	
	OR	None of these	and >3 of	5th finger clinodactyly
				Abnormal palmar crease
				Radial head dislocation/abnormal elbow extension
				Short 1st metacarpal/proximally placed thumb
				Bunion
				Partial 2,3 syndactyly toes
				Scoliosis
				Pectus excavatum
				Hip dislocation or dysplasia
(6) Neurosensory/ Skin	>3 of	Ptosis		
		Tear duct malformation or blepharitis		
		Myopia -6.00 D		
		Major eye malformation or peripapillary pigmentation		
		Deafness or hearing loss		
		Seizures		
		Cutis marmarata		
		Hirsutism, generalized		
		Small nipples and/or umbilicus		
(7) Other major systems	>3 of	Gastrointestinal malformation/malrotation		
		Diaphragmatic hernia		
		Gastroesophageal reflux disease		
		Cleft palate or submucous cleft palate		
		Congenital heart defect		
		Micropenis		
		Hypospadias		
		Cryptorchidism		
		Renal or urinary tract malformation		

OFC = head circumference. Diagnosis: (1) Positive mutation on CdLS gene testing; or (2) Facial findings and meet criteria from two of the growth, development or behavior categories; or (3) Facial findings and meet criteria for three other categories, including one from growth, development or behavior, and two from the other categories (see notes). Adapted from Kline AD et al. Cornelia de Lange syndrome: Clinical review, diagnostic and scoring systems, and Anticipatory guidance. *American journal of medical genetics part A* 2007; 143A: 1287-1296.

Table 2
Anesthetic Considerations in CdLS

Cardiac Anomalies	Provide endocarditis prophylaxis.
Pulmonary Anomalies	Increase risk of respiratory infections, irritable airway, hypoxia, and hypercapnia.
Renal dysfunction	Renally dose drugs
Airway	Risk of aspiration, and occlusion of airway. Prepare for difficult intubation.
Contraindicated drugs	Halothane and nitrous oxide
Recommended induction agents	Sevoflurane, isoflurane, ketamine, etomidate, and narcotics
Malignant Hyperthermia	Associated with paralysis in the presence of strabismus.

Cranio facial

Facial features are the most distinctive clinical feature. The head is microcephalic, with a low hairline on the forehead and posterior neck. Eyebrows are confluent and well defined, extend down to the nasal ridge and are highly arched in 98%[5]. Eyelashes are thick and long with an exaggerated upward curve of upper eyelashes and an exaggerated downward curve of bottom eyelashes. Hypertelorism and antimongoloid slant of the eyes are also noted. The midface has a flattened appearance with a short nose and anteverted nares. The nasal bridge is usually broad or depressed. The philtrum is long, smooth, and prominent, while the lips are thin with downturned corners. These patients also have micrognathia or square chin with a high arched palate and cleft palate in 30%[5]. Dental anomalies include widely spaced small teeth, absent teeth, and crowded teeth. Ears are low set, posteriorly rotated, and often hirsute.

Cardiovascular

The incidence of congenital heart disease is as high as 20 – 30%, compared to 0.8% for all births[5]. The most common abnormalities include (in descending order): ventricular septal defects, atrial septal defects, pulmonic stenosis, tetralogy of Fallot, hypoplastic left heart syndrome, and tricuspid aortic valve. Some heart defects have obvious signs and symptoms at birth that will prompt an evaluation by a pediatric cardiologist. Other defects are subtle and are not always recognized at birth; therefore detection of congenital heart disease in CdLS patients may be delayed. It is recommended that every CdLS patient be evaluated by echocardiogram.

Musculoskeletal

Along with the distinctive craniofacial features, specific extremity findings help in establishing a diagnosis of CdLS. Although lower extremity findings are less common, over 80% of affected individuals have partial syndactyly of toes 2 and 3[5]. Hands and feet are small in measurement in over 90%, and single palmar creases are observed in over 50%[5]. Fifth finger clinodactyly is observed in 74%, as well as bradydactyly[5]. The first metacarpal is usually disproportionately shortened with a proximally placed thumb[6]. Upper extremity malformations are observed in up to 30% of patients, and range from oligodactyly to ulnar deficiency to absent forearm, with digit(s) present distal to the elbow[6]. Other common extremity findings include radial head dislocation with abnormal elbow extension, clubbed feet and poikilothermia. Pectus excavatum, scoliosis and hip dislocation or dyplasia are other common musculoskeletal findings.

Gastrointestinal

Gastroesophageal reflux disease (GERD) is the most common GI complication in CdLS patients, with an incidence of over 90%[6]. Esophagitis, aspiration, chemical pneumonitis, and irritability are complications of GERD that can be avoided by diagnosis and treatment in the neonatal period. Pyloric stenosis has been reported, and may contribute to malnutrition and poor weight gain during the newborn period. Malrotation occurs in at least 10% and is associated with an increase risk of volvulus[6]. Congenital diaphragmatic hernia also occurs, however the reported incidence varies and may be underestimated secondary to infants who die in the perinatal period.

Genitourinary

Up to 40% of CdLS patients have structural kidney and/or urinary tract anomalies, the most

common are vesiculoureteral reflux, pelvic dilation and renal dysplasia, with the possibility of deficient renal function[6]. Genitalia malformations have also been reported in many CdLS cases. Crytorchidism has been reported in up to 73% of males, in addition to hypoplastic and micropenis in 57% and hypospadias[6]. Females may have small labia majora and abnormally formed uteri.

Auditory and Vision

Up to 60% of affected individuals have hearing loss, including both sensorineural and conductive[6]. Ear canals are narrow if not stenotic, which predisposes these patients to otits media and sinusitis[6]. The most common ophthalmologic findings are peripapillary pigmentations, high myopia, ptosis, microcornia, and blepharitis. Rare ophthalmologic findings include nasolacrimal duct obstruction, nystagmus, cataract and glaucoma.

Neuropsychiatric

Behavioral issues in CdLS patients are speculated to be secondary to frustration from an inability to communicate. Many individuals demonstrate behavior consistent with depression and attention deficit hyperactivity disorder, and display obsessive-compulsive behavior, autistic behavior, including self-destructive tendencies, defiance, extreme shyness and avoidance of social interactions.

Growth and Developmental Retardation

Growth failure occurs in over 95% of patients with CdLS[6]. Proportionate small stature begins prenatally, although most significant by six months of age, and continues throughout life. Although growth in CdLS parallels standard growth curves, mean height and weight remain below the 5th percentile[6]. Developmental delay is observed in over 95%[6]. Patients with classic CdLS experience profound to severe developmental delays. The overall IQ ranges from below 30 to 102, with an average of 53[7,8]. Patients with mild forms of CdLS have higher functioning with IQ ranging from normal to borderline IQ with learning disabilities[9]. However, most individuals experience disabilities in speech and language.

Anesthetic Considerations

Pharmacology

General anesthesia is often necessary in CdLS patients due to non-cooperative and hyperactive behavior. However, perioperative sedation should be light due the possibility of upper airway obstruction and unpredictable responses to drugs secondary to endocrine disorders[10]. In cases in which rapid induction of anesthesia is necessary, ketamine or etomidate are often recommended due to limited cardiac depressant effects [10]. In patients with suspected or confirmed pulmonary hypertension inhalational agents and narcotics are recommended[10]. Newer inhalation agents, including desflurane and sevoflurane, allow for faster recovery than older agents such as halothane. Nitrous oxide should be avoided since it can increase pulmonary vascular resistance[10]. Also, caution with induction of paralysis in patients with strabismus is warranted, as there is a reported association of malignant hyperthermia in these patients[10].

Cardiorespiratory

Preanesthetic examination to access for cardiorespiratory system is extremely important and often difficult. Many have previously undiagnosed congenital cardiac anomalies including tetralogy of Fallot, pulmonary or aortic stenosis, atrial septal defect, ventricular septal defect, pulmonary ductus arteriosus, hypoplasia of the left ventricle and abnormal electrocardiographic findings (i.e. AV block, left ventricular hypertrophy, and right ventricular hypertrophy) that are unveiled during anesthetic management. Cases of right bundle branch block, with and without murmur, first observed during anesthetic management have been reported[10]. Confirmation of any of these cardiac anomalies necessitates administration of antibiotics for endocarditis prohylaxis[10]. Postoperative complications in such patients include unstable cardiac function and marked susceptibility to infections. In patients with both cardiac anomalies and repeated episodes of upper airway obstruction secondary to macroglossia and micrognathia, pulmonary hypertension may develop, which may complicate anesthesia with the development of hypoxia and hypercapnia[10]. Successful perioperative

management of such cases may include increasing FiO2 to achieve adequate O2 saturations, and if warranted, prostaglandins, and even nitric oxide[10].

Pulmonary hypoplasia and lobular anomalies predispose CdLS patients to respiratory infections. The most common causes of death in such patients are acute pneumonia and bronchitis[11]. The airway is considered to be irritable and the administration of intravenous hydrocortisone has been shown to relieve asthma-like symptoms that occurred during general anesthesia[11].

Renal/Endocrine

Endocrine disorders and renal dysfunction, secondary to immaturity and malformation, necessitate preanesthetic evaluation to determine renal function and preparation for potential postoperative complications. Dosing of drugs excreted by the kidneys, should be carefully assessed.

Airway

Anesthetic management may pose a serious problem due to aspiration complications, and difficult intubation secondary to craniofacial anomalies characteristic of CdLS. The risk of aspiration secondary to GERD may be managed with premeditation including famotidine, metoclopramide and/or sodium bicitrate, and utilizing a rapid sequence induction with succinylcholine to offer some protection form stomach content aspiration.

Intubation in patients with CdLS almost always requires a tube of smaller size than that which is age appropriate due to the immature development of airway structures, most notably the presence of a hypoplastic larynx[11]. The craniofacial features that pose a risk of difficult intubation include macroglossia, cleft lip/palate, midface hypoplasia, high arched palate, and mandibular hypoplasia. In the case of macroglossia, the enlarged tongue fills the oral cavity, which obstructs the airway and impedes visualization of the larynx. Obstruction by the tongue can also occur in individuals with cleft palates. In this case, the nasal airway is obstructed if the tongue falls into the cleft, and oropharynx will be completely occluded if the tongue falls posteriorly with relaxation of the oropharyngeal musculature[12]. In midface hypoplasia, the palate is high and arched, and the nasal passages are small, therefore these individuals are primarily mouth breathers, which can potentially pose a problem during mask ventilation[12]. When the mouth is closed, the tongue occludes the small oral cavity and the small nasal passage creates resistance to nasal airflow, which can be overcome by holding the mouth open during induction[12]. Craniofacial dysostosis makes mask fit difficult; therefore maintaining a good mask seal is paramount[12]. In mandibular hypoplasia the anterior mandibular space is decreased, thereby decreasing the space into which the tongue is displaced during laryngoscopy, and making tracheal intubation more difficult[12]. Such patients should be managed with fiberoptic intubation, glide scope, or other advanced airway techniques. In general, difficult intubations encountered in CdLS are best managed by having an introducer, laryngeal mask or fiberoptic bronchoscope readily available. A laryngeal mask airway is recommended as an alternative to mask ventilation or tracheal intubation, and as a tool in fiberoptic scope assisted tracheal intubation[13]. Laryngeal mask airway is also beneficial in that it does not require paralysis, which may be relevant in individuals with strabismus, which can be associated with malignant hyperthermia[13]. Some literature advocates corticosteroid application prior to intubation to prevent airway trauma and edema from potential multiple intubation attempts[14].

Conclusion

Although specific gene mutations can be found in some patients, genetic testing is usually reserved to confirm an already highly suspected CdLS diagnosis. At present there is no cure for CdLS. Treatment is symptomatic and therapy based. Early intervention by means of medical and surgical care are necessary for feeding difficulties, congenital heart disease, urinary, auditory and visual abnormalities, as well as psychomotor delay. In summary, the anesthetic care of the patient with CDLS is often challenging and a well thought out perioperative plan can potentially reduce morbidity and mortality.

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