Goldenhar Syndrome: Cardiac Anesthesiologist’s Perspective

Abstract
Goldenhar syndrome or oculo-auriculo-vertebral dysplasia was defined by Goldenhar in 1952 and redefined by Grolin et al. later. As the name denotes, children with this syndrome present with craniofacial and vertebral anomalies which increase the risk of airway compromise. Neonates and infants with this syndrome often have premature internal organs, low birth weight, and airway disorders. For this reason, safe anaesthesia in such infants requires a complete knowledge regarding metabolism and side effects of the drugs. The association of cardiovascular abnormalities is not uncommon and possesses additional challenge for anesthetic management. The aim of this review is to draw attention to the various perioperative problems that can be faced in these infants when they undergo surgery or the correction of the underlying cardiac problem.

Keywords: Cardiovascular anaesthesia, goldenhar, oculo-auriculo-vertebral dysplasia

Introduction
The term Goldenhar syndrome, first coined by “Goldenhar,” is for the congenital hemicraniofacial dysmorphologies characterized by epibulbar dermoid, auricular appendices, and vertebral anomalies.[1,2] This is one of the most common congenital syndromes of first and second brachial arch.[2] Although the precise incidence of Goldenhar syndrome is not known, estimate range is from 1 in every 3500 to 1 in 5600 live births.[2] The term “Expanded Goldenhar Complex” described by various authors is associated with some uncommon but clinically remarkable associated anomalies.[3‑6] Cardiovascular malformations have been reported in 5%–58% of patients with Goldenhar syndrome. Most frequent is tetralogy of Fallot (TOF), followed by septal defects and situs inversus. This syndrome presents the anesthesiologist a dual challenge of difficult mask ventilation, difficult intubation, and compounded by other systemic defect. The risk increases further if the patient is an infant. The basic aim of this review is to share our own experience as well as to summarize the available evidences about the anesthesia management of these infants who underwent cardiac surgery. Case reports and bibliographies from these references were also reviewed. Although some articles are available when general anesthesia is concerned, there are only three case reports pertinent to cardiac anesthesia, and closed heart surgery exists in English literature.

Description of Cases
During the period from April 2002 till November 2016, we confronted 13 cases of Goldenhar syndrome who underwent surgery for the underlying cardiac problem. The diagnosis was made from Feingold M criteria, which included at least two of the following criteria: Eye abnormalities (lipomas/lipodermoid/epibulbar dermoid) in association with any of the followings, for example, ear, mandible, or vertebral anomalies.[7] The patients’ demographics, clinical picture supporting the syndrome, associated cardiovascular abnormalities, overall problems related to anesthesia, and postoperative complications are presented in Tables 1-3. Apart from the routine investigations as for any other pediatric cardiac surgical patients, all the patients underwent plain chest X-ray films including cervical to sacral spine. As most of the cases were done as emergency or semi-emergency and infants were small, flexion-extension views of the cervical

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spine and computed tomography (CT) of the spine were not feasible. Apart from the history pertinent to the cardiac problem, all the parents were asked regarding a clear history of snoring, noisy breathing, and stridor. A proper airway assessment was performed. All the routine investigations were done. Other congenital anomalies were ruled out. Various anesthetic approaches were discussed, and the possibility of a tracheostomy explained to the parents. We had kept backup facilities for a difficult intubation such as curved and straight laryngoscope blades’ sizes 1 and 2, endotracheal tubes (ETs) of smaller sizes, pediatric stylets, retrograde intubation kit, and fiber-optic bronchoscope. With potentially unstable hemodynamics resulting from anesthesia induction and airway manipulation, we designated one attending responsible for the airway, one for hemodynamics and anesthetic management, and the third one as an extra support in case of emergency. A resident anesthesiologist maintained manual in-line cervical stabilization throughout the procedure.

Different anesthesia techniques were followed depending on the patients’ condition. Apart from the routine monitoring for any other pediatric cardiac surgical patients, all the infants underwent a strict bispectral index monitoring for

| Table 1: Patients demographics and clinical picture |
|-----------------------------------------------|
| Patient number | Age (months) | Sex  | OA  | MD | MG | SB | AR | Scoliosis | Ocular anomaly |
| 1              | 3            | Female | HRP | −  | +  | +  | +  | −          | +              |
| 2              | 1            | Male   | CP  | −  | +  | −  | +  | −          | +              |
| 3              | 2.5          | Male   | −   | −  | +  | −  | −  | +          | +              |
| 4              | 8            | Male   | CL + CP | +  | +  | −  | −  | −          | +              |
| 5              | 11.0         | Male   | CL  | −  | −  | +  | +  | +          | +              |
| 6              | 10           | Female | −   | −  | +  | +  | −  | −          | +              |
| 7              | 12           | Male   | CP  | −  | +  | +  | −  | −          | +              |
| 8              | 12           | Male   | HRP | +  | +  | +  | +  | +          | +              |
| 9              | 4            | Male   | CP  | −  | −  | +  | −  | +          | +              |
| 10             | 5.5          | Female | −   | −  | +  | −  | +  | +          | +              |
| 11             | 8.5          | Female | −   | −  | +  | −  | +  | +          | +              |
| 12             | 14.5         | Female | HRP | +  | +  | −  | +  | +          | +              |
| 13             | 8            | Male   | CP + CL | +  | +  | −  | +  | +          | +              |

OA: Oral anomaly, MD: Mandibular dysplasia, MG: Micrognathia, SB: Spina bifida, AR: Absent radius, HRP: Horseradish peroxidase, CP: Cleft palate, CL: Cleft lip

| Table 2: Surgical procedure and problems during anesthesia induction |
|---------------------------------------------------------------|
| Patient number | Surgical diagnosis | Surgical procedure | Induction technique | Size of ETT/ route of administration | laryngoscope blade | Airway difficulty |
|----------------|--------------------|--------------------|---------------------|-------------------------------------|-------------------|------------------|
| 1              | VSD                | VSD closure        | I-Halo              | 3.5/O/UC                            | Straight          | Failed intubation |
| 2              | VSD, PAH           | PA banding         | I-Sevo              | 3/O/UC                              | Curved            |                  |
| 3              | TOF                | BT shunt           | I-Sevo              | 3/O/UC                              | Curved            |                  |
| 4              | VSD, PAH           | VSD closure        | I-Sevo              | Tracheostomy 4.5/C                   | Both              | Failed intubation |
| 5              | AVSD               | PA banding         | IV-Ket              | 4.5/O/UC                            | Curved            |                  |
| 6              | VSD                | VSD closure        | I-Sevo              | 4.5/O/UC                            | Curved            |                  |
| 7              | VSD                | VSD closure        | IV-Ket              | 3/O/C                               | Curved            |                  |
| 8              | DORV, VSD, PS      | Intracardiac repair | I-Sevo              | 3/O/C                               | Straight          | 5th attempt |
| 9              | AVSD               | AVSD closure       | I-Sevo              | Tracheostomy 3.5/C                   | Both              | Failed intubation |
| 10             | TOF                | BT shunt           | I-Sevo              | 4/O/UC                              | Curved            |                  |
| 11             | ASD                | Closure of the defect | I-Sevo              | Retrograde 4/N/UC                   | Curved            | Failed blind nasal and fiberoptic intubation |
| 12             | TOF                | Total correction   | I-Sevo              | 3.5/C                               | Straight          | Second attempt |
| 13             | TOF                | BT shunt           | I-Sevo              | 4/UC                                | Straight          | Third attempt |

ETT: Endotracheal tube, VSD: Ventricular septal defect, PAH: Pulmonary hypertension, AVSD: Atrioventricular septal defect, DORV: Double outlet right ventricle, PS: Pulmonary stenosis, TOF: Tetralogy of Fallot, ASD: Atrial septal defect, PA: Pulmonary artery, BT: Blalock-Taussig, Halo: Halothane, Sevo: Sevoflurane, Ket: Ketamine, O: Oral, UC: Uncuffed, IV: Intravenous, I: Inhalational
the assessment of depth of anesthesia to regulate anesthetic drug dosing. Case number 4 had high up larynx in spite of adequate mouth opening to pass a straight blade. The vocal cord was not visible even with optimum positioning and assistance. After failure of five attempts, a decision of tracheotomy was taken. Case number 9 had an unanticipated difficult intubation without the presence of any predisposing factors. This child too had an extreme degree of anterior larynx and underwent tracheostomy. Recurrent desaturation and bradycardia were occurred in both these infants during intubation attempt even though the mask ventilation was adequate. Both the infants needed postoperative nitric oxide therapy.

Case number 11 had extreme limitation of mouth opening where no space was left after insertion of the smallest size straight laryngoscope blade. Hence, the nasal route was the only remained option to secure the airway through the supraglottic path. Following three failed nasal intubation attempts, further plans for airway manipulation were aborted. Since it was possible to maintain the airway with a bag and mask while the infant was breathing spontaneously, retrograde intubation was attempted with the infant positioned supine with a shoulder roll and a head ring. The cricothyroid puncture was carried out under local anesthesia. An 18G intravenous needle was inserted into the cricothyroid membrane, and after confirming its position by aspiration of air, the needle hub was positioned cephalad. The guidewire of a triple lumen central venous catheter (20–22 size) was guided into the oral cavity with the bevel facing rostrally. The catheter was ultimately railroaded using a 6Fr infant feeding tube and brought out of the left nostril from the oral cavity. The rest of the length of the catheter was firmly secured and taped with an umbilical clamp after removing the 18G needle. The nasal end of the guidewire was tied to Murphy’s eye of a 4-mm uncuffed ET. After good lubrication, the tube was guided into the oropharynx and then pulled into the larynx, while firmly holding on to both ends of the guidewire. Once it was felt that the tube was beyond the vocal cords, placement was confirmed by breath sounds and a capnogram.

**Discussion**

The most comprehensive review of clinical manifestations of growth hormone (GH) syndrome was described Gorlin et al. in 1963. The term occulo-auriculo-vertebral dysplasia was introduced by him to describe patients with unilateral microtia, macrostomia, mandibular hypoplasia, vertebral anomalies, and epibulbar dermoids. Feingold and Baum’s later on listed the criteria for the diagnosis of this syndrome. Although the etiology of this disease is not fully understood, autosomal recessive or dominant inheritance is possible. The disease occurs as sporadic cases and has male predominance. The average incidence rate of this syndrome is estimated to be between 1:3000 and 1:5000 live births in different studies. The incidence of cardiovascular problem varies between 5% and 58% with TOF and ventricular septal defect as the most commonly reported heart defect. Association of interrupted arch and coarctation of the aorta has also been repeatedly reported. All our patients fulfilled the requisite diagnostic criteria. Ocular abnormality (lipoma/lipodermoid/epibulbar dermoid) was present in 100% of the cases. Nearly 60.5% cases had

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**Table 3: Postoperative problems**

| Patient number | Duration of mechanical ventilation (h) | Re-intubation | Duration of ICU stay (h) | Duration of hospital stay (day) | Complications if any |
|---------------|--------------------------------------|---------------|-------------------------|--------------------------------|----------------------|
| 1             | 78                                   | +             | 52                      | 8                              | Delayed extubation   |
| 2             | 12                                    | –             | 30                      | 6                              | –                    |
| 3             | 13                                    | –             | 30                      | 5                              | –                    |
| 4             | 120                                   | –             | 152                     | 21                             | Ventilator associated pneumonia, PA crisis |
| 5             | 14                                    | +             | 5                       | 12                             | Hemodynamic instability, readjustment of PA band |
| 6             | 3                                     | –             | 10                      | 4                              | –                    |
| 7             | 5                                     | –             | 10                      | 4                              | –                    |
| 8             | 10 (attempted but failed)             | 10            | 0.41                    | Accidental extubation          |
| 9             | 132                                   | Tracheotomy tube change twice | 168                     | 25                             | Recurrent PA crisis   |
| 10            | 83                                    | –             | 64                      | 9                              | Delayed extubation   |
| 11            | 1                                     | –             | 6                       | 4                              | –                    |
| 12            | 8                                     | –             | 24                      | 8                              | –                    |
| 13            | 14                                    | –             | 24                      | 7                              | –                    |

PA: Pulmonary artery, ICU: Intensive Care Unit
oral abnormalities. Mandibular dysplasia and microganthia were present in 30.7 and 84.6% cases, respectively. Nearly 60.2% infants had absent radius and 30% had scoliosis. Case number 1 and 10 had athyrosis which was diagnosed postsurgery during investigation of an unexplained delay in extubation.

Many attempts have been made to predict difficult laryngoscopy in pediatric patients. These methods have variable sensitivity in children. The Mallampati score, described by Cormack and Lehane, is not practical to use in infants due to poor cooperation. Standard values for thyromental and horizontal mandibular lengths do not exist for the pediatric population. We could be only able to assess mandibular space to predict difficult airways to some extent.[11] As all the patients in our series are below 2 years of age, it was not possible to go for a Wilson scoring system to predict the airway, thereby making us more prepared for the unanticipated difficulty during anesthesia induction.[11]

Knowledge of cervical vertebral embryology is instrumental in understanding the pathogenesis of vertebral developmental anomalies in Goldenhar syndrome. The neural tube forms early in the embryological development at 16–18 days of gestation, mesodermal cells condense in the midline to form notochordal process, and subsequently the notochord vertebral formation begins simultaneously when sclerotomal mesoderm forms the somites migrates toward the notochord. Chordification of the primitive vertebral column begins during the 6th week of gestation and ossification get complete at birth. However, fusion of spinous, articular, and transverse process is actually net complete until the 7th year of life.[12] Insults to the maturing embryo may occur in the form of intrauterine trauma, vascular insufficiency, or systemic teratogens. Inherited abnormalities can arise as the result of germline mutations involving molecular pathways critical for mesenchymal condensation and cartilaginous induction.[11]

Vertebral anomalies usually remain asymptomatic. However, apnea episodes can occur in some cases. Strict postoperative vigilance may prevent the episode of unexplained sudden respiratory arrest. Neurologic symptoms can arise from compression of brainstem cranial roots, nerves, spinal cord, or vertebral arteries. Apnea, dysphasia sensorineural hearing loss, nystagmus, suboccipital pain, syncope, transient visual loss, and acute episodes of quadriplegia can result as the child grows.

Vertebral anomalies are seen relatively commonly in Goldenhar syndrome. On the basis of this association, the general recommendation is these patients should have cervical spine imaging at the time of diagnosis or during early childhood. Most cervical vertebral anomalies can be detected by plane radiography if lateral and anterioposterior, often mouth and oblique, views are assessed, but obtaining this series of films in infant and toddler is difficult. CT provides excellent resolution and has become the imaging study of choice. Magnetic resonance imaging may complement CT scan by assessing compression of the brain and spinal cord. Children in whom vertebral anomalies are evident or even suspected should be referred to a neurosurgeon for evaluation and counseling on activity precaution. Unstable anomalies may require immobilization with a cervical collar or halls reduction and fusion. At times, even stable anomalies require surgical intervention to prevent progressive scoliosis and/or compensatory kyphosis.

Direct laryngoscopy and endotracheal intubation are exceedingly difficult in these patients; however, intubation with a flexible fiber-optic bronchoscope or management with laryngeal mask may obviate the difficulties. The association of vertebral anomalies in patients with GH syndrome warrants vertebral imaging in selected cases. However, flexion and extension films are only possible in child above 2 years of age. Narrowing of the spinal canal with cord compression due to moment of C1 in relation the C2 also requires surgical intervention.[14]

However, normal finding in imaging studies does not eliminate the risk of at atlanto-occipital subluxation upon relaxation of the cervical muscles under anesthesia, and all patients with GH syndrome should be managed as if they have cervical spine instability. The anesthesiologist must be familiar with the normal and altered bony and soft tissue anatomy in the airway due to various congenital disorders. Specific areas to assess during preoperative assessment include the oral cavity, anterior mandibular space, maxilla, temporomandibular joint, and vertebral column. The Schwartz hyoid maneuver measures the anteroposterior distance from the middle of inside of the mentum of the mandible to the hyoid bone and gives approximate idea of the potential space for laryngoscopy. A decrease in this space (normal about 3 cm in adults and 1.4–1.5 cm in the newborns) serves as a signal for the anesthesiologist to be prepared for difficult intubation. Unfortunately, even careful examination does not predict every case of difficult intubation so that unexpected problems may occur. There may also be difficulties in ventilating these patients with a face mask. Although we did not face any difficulty in mask ventilation in spite of the presence of micrognathia in some infants, difficulty in intubation was happened in five cases. In our case, the difficulty with tracheal intubation was far greater than the problem in maintaining a patent airway. Marked micrognathia hampered insertion of a smallest straight laryngoscope blade in one of the cases. Mandibular hypoplasia in combination with high-arched palate made visualization of glottis impossible. It is difficult to explain the short distant at which the tube had to be secured. Auscultation method in combination with pulse oximetry is mandatory to confirm the correct placement.

Different induction techniques had been tried by different authors without any squeal. Regarding the use of induction
agents, Madan et al. found that intravenous induction was preferable to the gaseous one. Choice of maintenance agents in these children varies with the type and duration of surgery. As most of the patients are premature and have a possibility of postoperative apnea, hypothermia, and decreased metabolism of the drugs are common. Therefore, an inhalational anesthesia or propofol is advocated by some authors.[17,18] Cardiac surgical patients at most of the time need some duration of postoperative ventilation and have a longer surgical time as well as the stress response is more; hence, a combination of intravenous with an inhalational agent is preferred. Due to a compromised cardiovascular system, propofol and sole inhalational agents cannot be preferred because of their myocardial depressant property.[19] Most of our patients were induced with sevoflurane and maintained with a combination of midazolam and fentanyl.

Permanent thyroid deficiency at times presents since birth in patients with GH syndrome. Clinical manifestations are subtle ant usually not present at birth, probably as a result of transplacental passage of some maternal thyroid hormone.[19] Moreover, specific signs and symptoms do not develop since several months of age. Common clinical features and signs include decreased activity, increased sleep, feeding difficulty, and constipation. As these symptoms are also common in congenital cardiac defect, it is difficult to rule out this problem clinically. Prolong jaundice, myxedematous facies, large posterior fontanelle, macroglossia, and a distended abdomen is the usual symptoms, however, were insignificant in our patients. Due to extreme low age and associated cardiac problem, appreciation of hypotonia was missed in our infants. Goiter is always absent, thus making the clinical diagnosis more difficult. An unusual and unexplained delay in extubation in our infants raised the suspicion of athyreosis. A high TSH and low T4 level confirmed the diagnosis. Levothyroxine was started at a dose of 50 µg/kg/day after an endocrine consultation, and the infants were extubated subsequently without facing further problem during hospital stay.

Recurrent bradycardia and hypoxemia in case number 4 and 9 can be explained by the precipitation of pulmonary artery hypertensive crisis (PAH) in these infants due to the presence of noxious stimulus. These groups of patients at times may land up in severe right ventricular (RV) failure. The increased wall tension in RV reduces coronary perfusion, leading to ischemia and possible cardiac arrest if not treated urgently. We kept all the resuscitation measures ready to deal with such a situation. An echocardiogram during acute PAH crisis demonstrates a dilated, poorly contractile RV and underfilled left ventricle. As emergency echocardiogram is not feasible during intubation attempt, management should go along with the clinical suspicion. Both the patients received phenoxybenzamine at a dose of 0.5 mg/kg postanesthesia induction, nitric oxide from weaning off bypass till the 4th postoperative day. The incidence of PAH-related cardiac arrest in the operating room is 117 per 10,000 anesthetics, and the overall mortality is 0.78%. Hence, the significance of this problem and the therapeutic armamentarium available to manage PAH in the perioperative period is essential for all anesthesiologists treating these children. A close collaboration between anesthesiologist, cardiac surgeon, cardiologist, and operating room assistance is essential throughout the procedure and during a hospital stay.

Conclusion

Patients with this rare syndrome present a challenge to the cardiac anesthesiologist. The perioperative management for the cardiac surgical patients suffering from GH syndrome depends on the type, extent, and severity of craniofacial vertebral anomalies, severity of cardiovascular problem, underlying metabolic abnormality, and nature of surgery. In case of elective surgery, these cases call for a thorough evaluation, investigation, and preparation. During emergency though every possible investigation is not feasible, the team should have a detailed awareness about the disease and possible problems that can arise during the perioperative period. A call for additional help should be respected. The airway management should be tailored to the available measures.

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Conflicts of interest

There are no conflicts of interest.

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