Impact of Micro- and Retrognathia on the Neonatal Airway

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Etiology and Background

The human mandible is a unique structure that undergoes considerable anatomic changes during growth and development. In the neonatal period, the mandible is flat, with a short ramus, and poorly defined articulation with the skull base [1]. It is, therefore, prone to retroposition (retrognathia) which, when combined with insufficient mandibular sagittal projection (micrognathia), can result in posterior-inferior positioning of the tongue base. Because the tongue is anchored to the mandible, micro- or retrognathia forces the tongue posteriorly into the oropharynx and can lead to its displacement into the hypopharynx (glossoptosis) resulting in severe tongue-base obstruction of the supraglottic airway (Fig. 1).

The triad of micrognathia, glossoptosis, and tongue-based airway obstruction (TBAO) was initially described in 1939 by Dr. Pierre Robin, a French somatologist, who implicated the small mandible as the causative deformity leading ultimately to airway compromise [2, 3]. This "domino" effect is therefore known as Pierre Robin sequence (PRS). A sequence is constellation of abnormalities which are linked from an inciting anomaly or deformity. In the case of Pierre Robin sequence, failure of normal mandibular development sets off a cascade of anatomic changes in utero which result in the varying and seemingly unrelated physical findings (Fig. 2). {Figueroa 1991}.

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The etiology of this mandibular deformity is the topic of much debate. Several studies have attributed the micrognathia seen in Pierre Robin sequence to intrauterine deformation or extrinsic factors rather than intrinsic growth restriction of the mandible itself [4]. From between the 6th to 12th week of gestation, the human embryo transitions from a position of extreme neck flexion where the mandible is buried in the upper thorax to a position of gradual extension [5]. This period coincides with rapid mandibular growth that allows the tongue to descend and the palatal shelves to fuse. Several factors including multiple gestation, oligohydramnios, and cervical hemivertebrae may restrict this extension [6]. These studies point to the phenomenon of "catch-up growth" as evidence that extrinsic compression plays an important role in the deformity.

Increasingly, attention has focused on genetic cause of PRS. In addition to the syndrome-associated cases of PRS such as those patients with Stickler or Treacher Collins syndromes who demonstrate intrinsic mandibular growth deficiency, non-syndromic PRS may also have a genetic component. Investigators have demonstrated increased frequency of palatal clefts in the parents of patients with PRS [7] as well as several novel genetic mutations present in a proportion of such patients [8, 9].

No matter the cause, PRS is a challenging disease process which can result in acute airway compromise, chronic obstructive sleep apnea, cor pulmonale, anoxic brain injury, and even death [10]. In the neonatal period, this entity can be particularly devastating, often necessitating emergent postnatal intubation in severe cases. Even in patients who do not require emergent airway management, chronic hypoxia, feeding intolerance, and failure to thrive may be common [11]. In one of Pierre Robin's early publications, he describes the grim prognosis of a severely affected child: "I have never seen a child live more than 16–18 months who presented hypoplasia as such the lower maxilla was pushed more than 1 cm behind the upper"[2].

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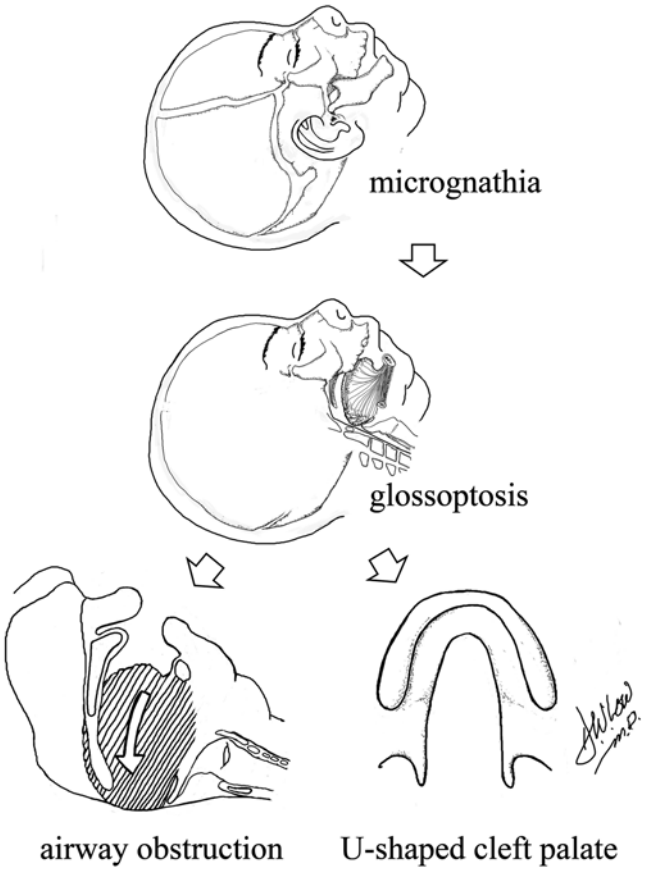

Fig. 1 The "domino effect" of Pierre Robin sequence (Courtesy of David Low, MD)

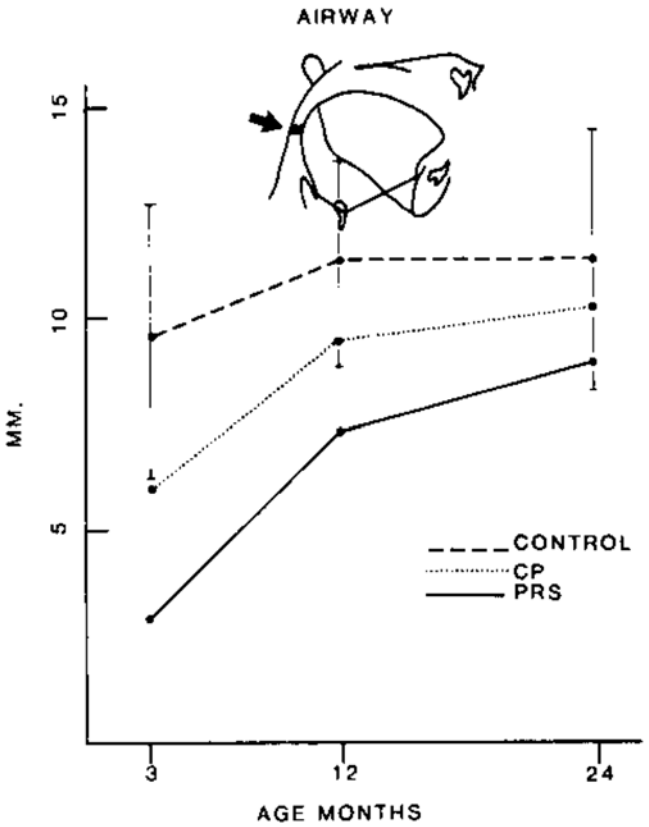

Fig. 2 Catch-up growth (Reprinted from [40] Permission granted from Allen Press Publishing Services)

History and Epidemiology

Congenital micrognathia is associated with over 100 known syndromes [12]; however, in the setting of tongue-based airway obstruction as is seen with Pierre Robin sequence, it is estimated to occur in 1 in 8,500 to 1 in 14,000 live births [13]. In 40–60 % of cases, PRS occurs in isolation, as the only disease process. However, over half of patients may carry syndromic diagnoses which not only play a role in disease pathogenesis but may contribute to increased disease severity. The most common of these associated syndromes, for example, is Stickler syndrome, which has prevalence of 1 in 8,000 live births in the general population but is present in over 30 % of patients with PRS. Table 1 lists several of the major syndromes commonly associated with PRS.

Table 1 Frequency of associated syndromes

	Frequency in general population[a]	Frequency in Robin sequence[b]
Stickler	1:8,000	1:3
Velocardiofacial Syndrome	1:2,000	1:9
Fetal alcohol	1:1,000	1:10
Treacher Collins Syndrome	1:25,000	1:20
Undefined syndrome	–	1:3

[a]Per live births
[b]Per patients with Robin sequence

Classification

There is no widely accepted classification system to stratify disease severity in patients with Pierre Robin sequence. As mentioned previously, several studies have associated worse outcomes in PRS patients who also carry syndromic diagnoses, and most centers now routinely recommend genetic screening after diagnosis. However, there is a wide variability in the severity of many syndromic diagnoses, and the simple presence or absence of a syndrome, alone, does little to differentiate such patients. Patients with Stickler or Nager syndromes often have more severe presentations than in PRS patients without accompanying syndromes, whereas many syndromes seen in these patients may contribute little or not at all to disease severity. Although many studies demonstrate worse outcomes in syndromic PRS as a whole, we caution against making management decisions based solely on the presence or absence of a syndrome.

Indeed, the key to differentiating the impact of micrognathia on the neonatal airway is to quantify its degree of deformity,

Table 2 GILLS scoring system for tongue-based airway obstruction

	GILLS Criteria
1	Presence of GER
2	Preoperative intubation
3	Late presentation (>2 weeks old)
4	Low birth weight (<2,500 g)
5	Syndromic diagnosis

Greater than two of these criteria correlate with high failure of Tongue-lip Adhesion surgery {Rogers 2011; Abramowicz 2012}

and those syndromes which adversely affect outcomes in Pierre Robin sequence are all associated with macroglossia or micrognathia. In order to assess the severity of anatomic mandibular deficiency, several authors advocate for the measurement of maxillary-mandibular discrepancy (MMD) as a simple, reliable, and reproducible method for stratification [14]. From the "worms eye" position looking superiorly, the mandible is gently closed to the maxilla and the distance between the midline mandibular alveoli and maxillary alveoli is measured. The realization that maxillary projection may also be inadequate in some forms of PRS, however, limits the utility of this tool [15]. In contrast, others recommend a clinical grading scale based on the severity of airway compromise [16].

The only validated classification system for patients with Pierre Robin system was developed as a means of determining which patients would benefit from surgical intervention. The GILLS criteria [17, 18] assesses for the presence of five factors which are shown to predict which patients might benefit from tongue-lip adhesion (TLA) surgery and which patients required direct tracheostomy (Table 2). Those patients with scores of two or less had a 100 % chance of success with the procedure whereas those patients with scores of three or more had close to a 50 % failure rate requiring tracheostomy.

Clinical Presentation

As stated previously, patients with Pierre Robin sequence demonstrate a wide spectrum of disease severity ranging from subclinical presentation to frank life-threatening respiratory compromise. Although the degree of micrognathia plays an important role in the development of respiratory symptoms, this is often a subtle finding in the neonatal period and observation for clinical signs of distress is imperative.

In the immediate postnatal period, patients with severe forms of Pierre Robin sequence will often display signs of distress such as grunting and crying, obvious apneic episodes, and even cyanosis. Those less severely affected may demonstrate increased work of breathing including supra- and substernal and intercostal retractions as well as cervical hyperextension. Symptoms are often positional with some improvement in prone position. Some neonates show few signs of respiratory compromise while awake. However, as resting tone decreases during phases of deep sleep, the tongue may assume a more posterior posture leading to obstruction.

In the first weeks of life, patients with moderate obstruction may present during an initial well child visit with inadequate weight gain, cachexia, or even failure to thrive sometimes without a history of apneic events. There are several reasons for feeding difficulties in PRS. First, the small mandible and tongue malposition as well as the presence of a palatal cleft pose significant physical restrictions on infant suckling. Indeed, primary oropharyngeal dysmotility has been noted in some patients. Second, feeding in infancy poses substantial metabolic demands, and patients with subnormal oxygenation may present with "exercise-induced" anorexia. Finally, gastroesophageal reflux (GER), although common in many infants, is especially challenging in those with Robin sequence with a reported incidence as high as 85 %. [19] As the tongue falls back, infants may increase inspiratory pressures in order to overcome the obstruction. The increased negative intrathoracic pressure then overcomes lower esophageal sphincter tone, and the gastric contents are "sucked" into the esophagus and the bronchial tree [6]. Such subclinical aspiration can be a substantial source of morbidity.

Cleft palate, although not a diagnostic criteria, occurs in the majority of patients with PRS, so much so that it is often incorrectly included among its essential characteristics. It is, however, distinct from other forms of palatal clefting with or without cleft lip [20]. The cleft palate associated with Pierre Robin sequence most often is wide and U-shaped, a result of failure of the palatal shelves to fuse in early gestation (8–12 weeks) due to the presence of an abnormally positioned tongue.

Evaluation and Clinical Approach

Timely multidisciplinary team evaluation—including Neonatology, Genetics, Pulmonology, Otolaryngology, the Feeding Team, and Plastic Surgery—is essential to maintaining adequate oxygenation and weight gain in patients with Pierre Robin sequence. A thorough history and physical exam should be performed to assess for potential syndromic association as well as evaluate overall appearance and tone. Indeed, hypotonia has the potential to exacerbate airway obstruction in affected patients and, in severe cases, may suggest poor response to interventions which address the upper airway. A complete airway exam is also an imperative first step in evaluation to determine the need for adjunctive airway support including high flow supplemental oxygen, continuous positive airway pressure, and intubation if necessary. Continuous pulse-oxymetry should also be employed early on in order to fully evaluate the number and degree of obstructive events.

Plain lateral radiographs with soft tissue windows may help characterize degree of micrognathia as well as assess

for severity of glossoptosis by allowing for visualization of a patent or occluded airway stripe. In neonates the airway stripe should measure approximately 4 mm [21]. Although such an evaluation may provide insight into the degree of upper airway compromise, it is not substitution for direct visualization of the airway.

Bedside fiberoptic naso-endoscopy is an important tool to localize the level of airway obstruction and should be performed prior to any definitive intervention. In addition to a noninvasive way to visualize the lower airway, endoscopic evaluation of the entirety of the upper airway can rule out other causes of obstruction such as choanal atresia. Additionally, direct micro-laryngo-bronchoscopy (MLB) is essential to evaluate subglottic structures and to rule out the presence of laryngomalacia, tracheomalacia, and other pathologies [22]. A jaw-thrust maneuver performed under anesthesia at the time of MLB can help determine the extent to which mandibular advancement can improve tongue base position. Presence of lower airway pathology may significantly alter management decisions.

Diagnosis

The diagnosis of Pierre Robin sequence relies on the clinical finding of micrognathia in the setting of tongue-based airway obstruction. Although the presence of micrognathia is easy to establish on exam, and airway obstruction is readily apparent in severe cases, the extent to which the tongue base contributes to airway compromise can be difficult to determine. For this reason, diagnostic airway endoscopy is essential to confirm the presence of glossoptosis and rule out other sources of upper or lower airway obstruction.

Mild to moderate cases of Pierre Robin sequence, however, where profound desaturation and cyanosis are often absent, present diagnostic challenges to clinicians. In these settings, polysomnography (PSG) has been utilized to establish and characterize the presence of apneic events and to quantify the frequency and degree of airway obstruction [14]. Sixteen lead polysomnography, in particular offers a thorough evaluation of neonatal sleep and respiratory function. It consists of electroencephalographic, electrooculographic, electromyographic, electrocardiographic monitoring as well as detailed analysis of respiratory performance and tissue oxygenation throughout the sleep cycle. It is utilized to quantify the number of apnea and hypopnea events per hour (apnea–hypopnea index) as well as the severity of obstruction as measured through oxygen saturation and end tidal and transcutaneous carbon dioxide measurements (Fig. 3). Indeed, PSG plays an important role in establishing the presence of subtle obstructive events that may be overlooked clinically during wakefulness and is crucial for quantifying the severity of airway obstruction during sleep [23–25]. Additionally, PSG can differentiate central apneas secondary to brainstem dysfunction and the obstructive events that may be improved with intervention. Many practitioners now advocate for an expanded role for polysomnography beyond mild presentations of the disease citing its utility as an objective way to measure improvement after airway interventions.

Management

Neonates with tongue-based airway obstruction represent therapeutic challenges to caregivers, in part because of the diagnostic difficulties that exist for these complex patients. Another source of difficulty is the relatively poor outcomes data available to provide an evidence-based treatment framework, especially for severely affected patients. Although numerous authors have published treatment algorithms for the management of Pierre Robin sequence, prospective comparative studies are lacking. A recent systematic review of the literature highlights the dearth of high quality evidence related to the management of this challenging patient population [26]. In 126 peer-reviewed articles published between 1980 and 2010, the authors found few studies utilizing standardized diagnostic criteria, therapeutic algorithms, or outcomes measures making side-by-side comparison difficult. Nonetheless, because the repercussions of therapeutic failure so are great for patient with Pierre Robin sequence, including anoxic brain injury, cardiac and pulmonary dysfunction, malnutrition and even death, the stakes of adequate management are extremely high.

Any therapy should be tailored to the individual needs of the patient and particular concerns of the family. The gold standard treatment of TBAO has historically been tracheostomy, as this is the only intervention that completely bypasses the tongue base as the source of obstruction. However, given this procedure's high associated cost, morbidity, and mortality [27], many alternative treatment modalities have been investigated, including nonsurgical remedies such as prone positioning or nasopharyngeal airways (NPA) as well as surgical interventions such as tongue-lip adhesion (TLA) and mandibular distraction osteogenesis (MDO). No matter what treatment is planned in order to address the airway obstruction in Pierre Robin sequence, nutritional supplementation with oral, nasogastric, or gastrostomy feeding is essential to maximize growth and development.

The first-line therapy for patients with Pierre Robin sequence is conservative airway management including supplemental oxygen and positioning. Prone positioning of the patient allows the mandible and tongue to fall forward and out of the posterior pharynx, serving to minimize the obstruction caused by the tongue base. Positioning, however, requires constant vigilance and may make already tenuous feeding more difficult. It also places considerable stress on family and caregivers. Additionally, a nasopharyngeal airway

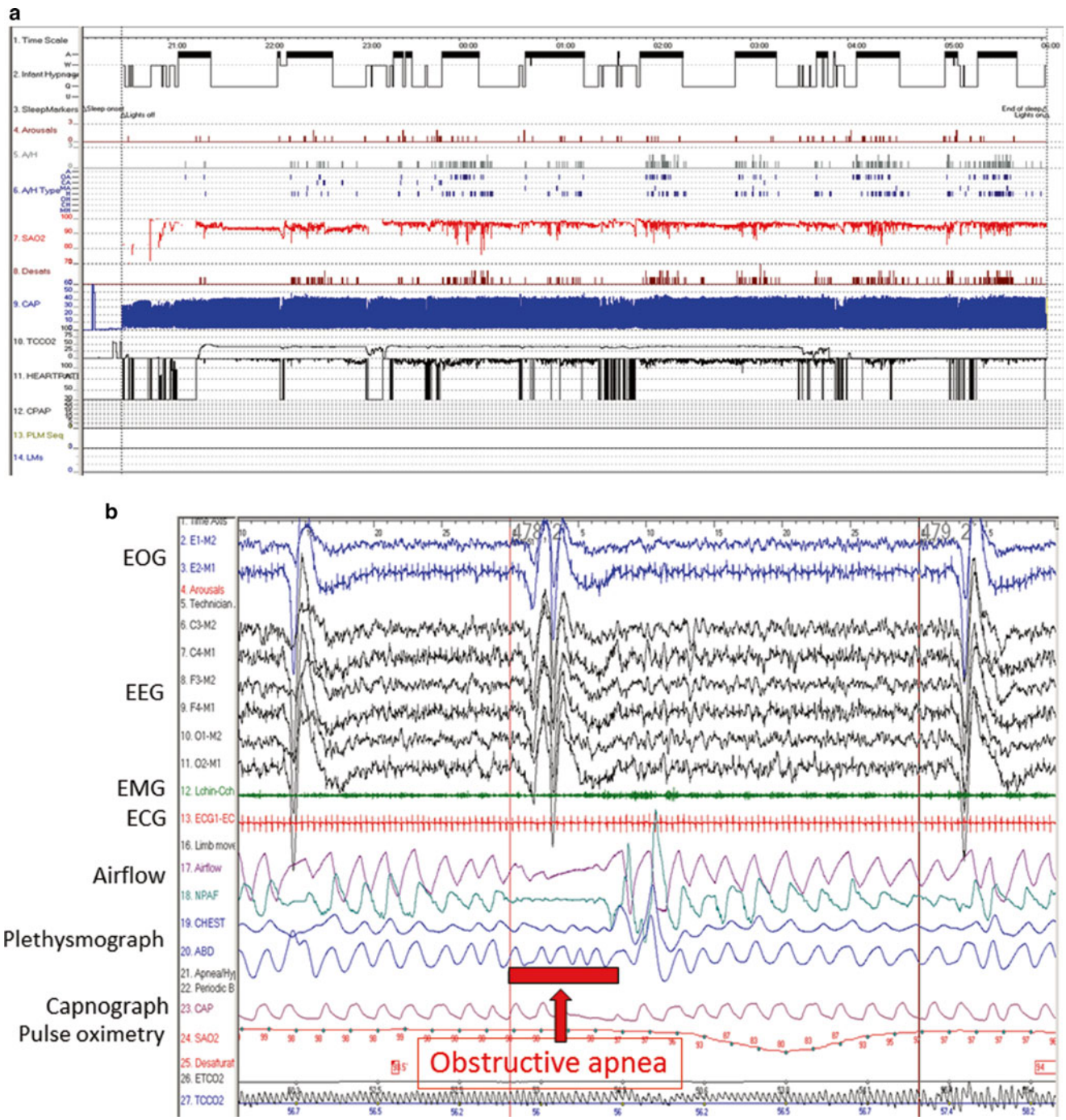

Fig. 3 (**a**)17 channel polysomnogram used to evaluate for occult obstructive apnea often seen in tongue based obstruction in neonates with micrognathia. (**b**) A closer view of the 17 channel extensive polysomnogram showing obstructive apnea in a more magnified view of airflow disruption with resultant desaturation in an infant with micrognathia. (Courtesy of Christopher Cielo, Pulmonary Medicine, The Children's Hospital of Philadelphia)

(NPA) can be fashioned from a small endotracheal tube and placed at the bedside without anesthesia. The NPA must be long enough to extend beyond the obstructing tongue base so that it can help push the retropositioned tongue out of posterior pharynx and relieve any obstruction [28, 29]. A final avenue for conservative treatment is prolonged intubation, a period of several weeks, in order to allow for improved airway tone and mandibular growth. Taken together, the success of these conservative measures has been reported to be between 50 and 85 % of patients [30–32].

Surgical intervention should be considered for persistent or severe airway obstruction that has failed or is not amenable to conservative treatment alone. The three main options for surgical airway correction include tongue-lip adhesion

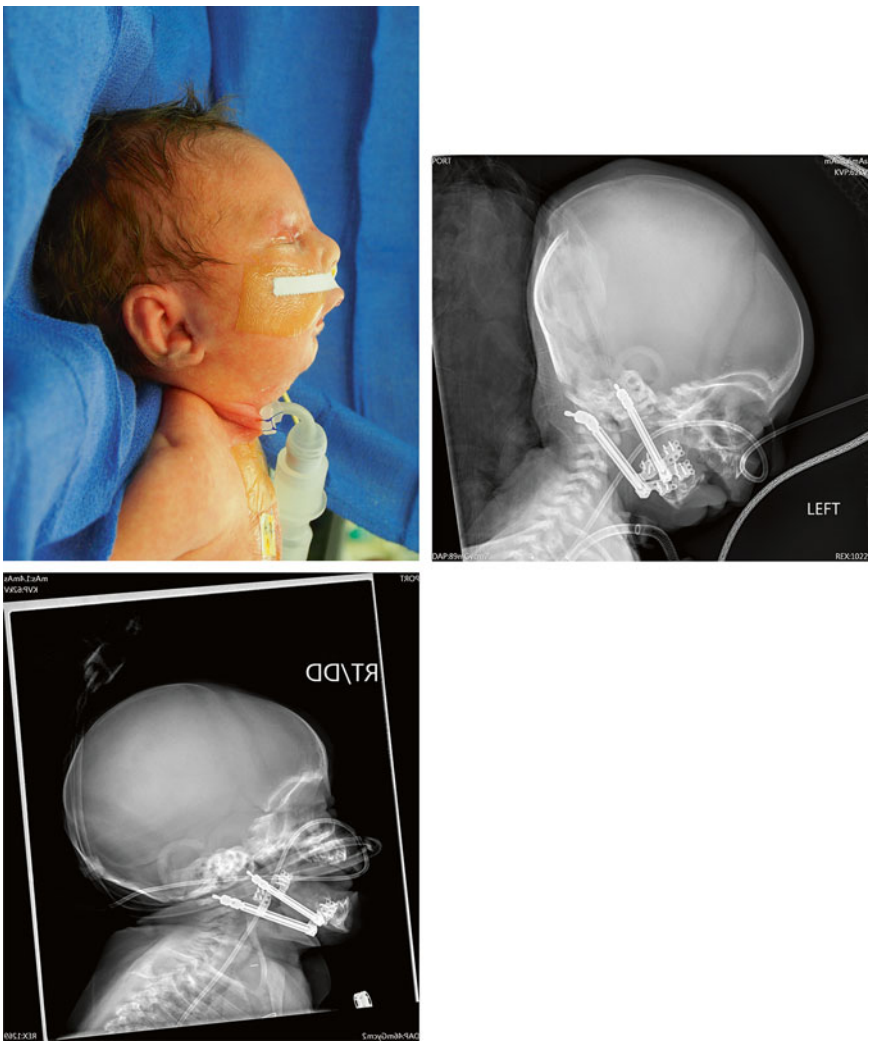

Fig. 4 (**a**–**d**) Pre- and postoperative photographs of patient undergoing mandibular distraction osteogenesis through a submandibular approach

(TLA), mandibular distraction osteogenesis (MDO), and tracheostomy.

Tongue-lip adhesion has been utilized for the treatment of airway obstruction associated with micrognathia for close to six decades [33]. Although variations of the procedure exist, in its simplest form, TLA approximates the muscularis proprious of the tongue and ventral mucosa to the mentalis muscle and labial mucosa. Variations include placing a permanent circum-mandibular retention suture through the body of the tongue itself. All iterations of the procedure serve to bring the tongue into a more anterior position in the mouth, preventing glossoptosis. This adhesion is left in place during the first 6–12 months of life to allow for mandibular and airway growth prior to its surgical reversal. Several centers have published on their experience using TLA as a first-line surgical treatment for patients who fail conservative management [17, 34–36]. They cite success rates ranging from 73 to 90 % while complications range from 10 to 55 %. Historically, TLA has been the most utilized surgical procedure to avoid tracheostomy in patients with PRS.

The introduction of mandibular distraction osteogenesis (MDO) to the surgical armamentarium for the treatment of Pierre Robin sequence over a decade ago has increased the treatment options for these complicated patients [37]. Although it has been over two decades since McCarthy et al. applied the principles of distraction osteogenesis to the mandible, {Mccarthy 1992} MDO has only recently developed traction as an effective and easily applied technique. Indeed, MDO remains the only currently available treatment modality that directly addresses micrognathia in patients with PRS.

In the procedure, the mandible is accessed bilaterally either through intraoral or submandibular incisions and mandibular osteotomies are made through the mandibular body. Internal or external distraction devices are then applied. After a short latency period, the devices are activated, slowly

separating the mandibular segments at a rate of 1 mm/day. Once the desired advancement has been achieved, the devices are left in position for 6–8 weeks until the new space has re-ossified at which time the devices are removed.

Since its first description in 2002, only a handful of studies have been published with rigorous outcomes metrics assessing the efficacy of MDO. In two such retrospective studies, the authors report on a total of 57 patients with TBAO. {Hammoudeh 2012} (Goldstein, et al. PRS submitted 2013) Both studies demonstrate the improvement in airway parameters as measured by PSG after surgery while failure of MDO ranged from 3 to 14 % and surgical complications ranged from 14 to 28 %.

Although successful and safe, MDO is not without risks. Injury to the inferior alveolar nerve as well as developing tooth buds may theoretically occur, but long-term analyses are lacking to adequately assess such risks. Both techniques are associated with scaring, however, with the submandibular approach, such scars are generally acceptable and well hidden (Fig. 4 a–d). Additionally, there are currently no long-term data indicating the effect of MDO on mandibular growth, although growth restriction may be difficult to distinguish from that inherent to PRS itself.

Multidisciplinary Considerations

As mentioned previously, the assessment, diagnosis, and management of patients with Pierre Robin sequence requires significant input from a multitude of specialists. These infants, therefore, should be evaluated in a team setting to assess the anatomic and genetic findings, determine the cause of airway obstruction, educate caregivers on conservative measures including positioning and feeding protocols, and establish a course of treatment which minimizes obstructive events and burden to patient and family alike [6, 38]. Such a multidisciplinary team should consist of specialists from craniofacial and plastic and reconstructive surgery, pediatric/neonatal intensive care, pediatric otolaryngology, pulmonology, anesthesia, nursing, speech pathology, and genetics [30].

Future Considerations

Our understanding of Pierre Robin sequence is rapidly evolving due to improved diagnosis and treatment modalities. A better grasp of nonsurgical and surgical approaches to management has been achieved by an improved ability to characterize disease severity and accompanying disorders in these patients. As we continue to better stratify patients into more meaningful risk groups, and long-term prospective studies are performed, a cohesive treatment algorithm will begin to emerge which may help reduce the burden of care for patients, number of procedures, and time to adequate treatment in this challenging patient population.

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