Pierre Robin Sequence: Challenges in the Evaluation, Management and the Role of Early Distraction Osteogenesis

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Background: The challenges for the management of Pierre Robin Sequence (PRS) are the evaluation and management of airway and feeding difficulty from glossoptosis and associated cleft palate.

Objective: To present the clinical findings, management, outcome and the role of early distraction osteogenesis in patients with PRS.

Material and Method: The medical records were reviewed of patients with PRS seen and managed by the authors at Srinagarind Hospital, Khon Kaen University between 2001 and 2011.

Results: Fifteen patients with PRS were seen and managed. The female-to male ratio was 1.8 to 1 (9 girls, 5 boys). All of the patients presented with a small mandible, retrodisplaced tongue and upper airway difficulty. One patient had cleft lip only and one patient had cleft lip with cleft palate. Patients were primarily from the provinces of Khon Kaen and Mahasarakham. Conservative management was successful in 12 patients while the 3 with tracheostomy required distraction osteogenesis and the tracheostomy was subsequently successfully decanualted. At the last follow-up, most of the patients had proper catch-up and mandibular growth.

Conclusion: Primary management of airway insufficiency in patients with PRS can be managed in a prone position with or without nasopharyngeal airway, prolonged intubation, tongue-lip adhesion, mandibular distraction osteogenesis and tracheostomy. The present study confirmed that proper conservative management can be used to manage most of the patients with PRS. However, early mandibular distraction should be considered when (a) indicated in patients with respiratory insufficiency to avoid tracheostomies or (b) successfully decannulating tracheostomies. Interdisciplinary team management is needed to ensure proper evaluation, improve care and optimum outcome.

Keywords: Pierre Robin Sequence, Airway and feeding difficulty, Mandibular distraction osteogenesis, Interdisciplinary management

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In 1923, Pierre Robin described the Pierre Robin Sequence (PRS) as a characteristic of neonates with small mandibles (micrognathia), posterior displacement or retraction of the tongue (glossoptosis), and upper airway obstruction(1) and in 1929 he added cleft palate deformity as an associated feature(2). The sequence is defined as “a pattern of multiple anomalies derived from a single known or presumed prior anomaly or mechanical factors”(3).

The reported incidence of PRS varies between 1 in 5,000 and 1 in 50,000. The etiology of PRS is multifactorial and may depend upon the cause of associated syndrome(s), associated abnormalities, or the mandibular deformities(4). With severe micrognathia, glossoptosis develops due to the relative position of the tongue due to the retropositioned or hypoplastic mandible. PRS is described as a sequence and not a syndrome as it is attributed to the sequence of events that occur during embryogenic development(5) and may be classified as non syndromic or syndromic. Most (82%) patients with PRS have multiple associated anomalies or syndromes(6,8) or PRS may be a component
of syndromes in which the micrognathia deformity is expressed\(^6,9\). Spranger et al reported that over 40 syndromes have been described in association with PRS (the most common being the Stickler syndrome) and 55% of the patients did not have a syndromic diagnosis\(^3\).

The important clinical finding in patients with PRS are (a) airway obstruction from the hypoplastic mandible and the posteriorly displaced tongue (b) increased risk of aspiration and (c) compromised ability to feed. The U-shaped, cleft palate may be associated with a hypoplastic mandible disrupting normal palatal development\(^4\).

The challenges for management of PRS are the evaluation and management of airway and feeding difficulty from glossoptosis and associated cleft palate. The objective of the present study was to present the clinical findings, managements, outcomes and the role of early distraction osteogenesis in patients with PRS.

Material and Method

**Setting**

Srinagarind Hospital is the main tertiary care, university hospital for the northeast of Thailand. The Northeast is the poorest region of the nation, with a population of about 22 million.

**Study design**

The authors reviewed the medical records of the patients with PRS seen and managed at Srinagarind Hospital, Khon Kaen University between 2001 and 2011. The diagnosis of PRS was based upon clinical findings of small mandibles (micrognathia), posterior displacement or a retropositioned tongue (glossoptosis), and upper airway obstruction. An associated U-shaped cleft palate may also have been presented. Details of the clinical findings, radiologic records, nonsurgical and surgical management, and outcome were analyzed.

The protocol of the present study was reviewed and approved by the Ethics Committee of Khon Kaen University, according to the standards set out in the Helsinki Declaration. Written informed consent was obtained from each patient.

**Results**

Between 2001 and 2011, 15 patients with PRS were seen and managed by the authors. The female-to-male ratio was 1.8 to 1 [9 girls (F) and 5 boys (M)]. All of the patients presented with a small mandible, a retrodisplaced tongue and upper airway difficulty. Most of the patients also had a U-shaped cleft palate. One patient had a cleft lip only and one patient had a cleft lip with a cleft palate. Table 1 presents the demographic details and Fig. 1 the geographic distribution of these 15 patients. Most of the patients came from the provinces of Khon Kaen and Mahasarakham. Conservative management was successful in 12 patients while in three distraction osteogenesis was performed because they had a tracheostomy which was later successfully decannulated. At the last follow-up, most of the patients had proper catch-up and mandibular growth.

**Patient report**

**Patient No. 7**

A female patient, born in 2004 in Mukdahan province, was referred from Mukdaharn Hospital with...
Table 1. Details of 15 patients with Pierre Robin Sequence (PRS) treated at Srinagarind Hospital, Khon Kaen University, between 2001 and 2011

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Year of birth</th>
<th>Province</th>
<th>Clinical Findings</th>
<th>Treatment/operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>1980</td>
<td>Maha Sarakham</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Secondary Furlow palatoplasty and speech management</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>2001</td>
<td>Chaiyaphum</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Palatoplasty</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>2001</td>
<td>Nong Bua Lam Phu</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Palatoplasty</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>2001</td>
<td>Kalasin</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Cheiloplasty and palatoplasty</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>2002</td>
<td>Khon Kaen</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Palatoplasty</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>2003</td>
<td>Kalasin</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Palatoplasty</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>2004</td>
<td>Mukdahan</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Palatoplasty</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>2003</td>
<td>Maha Sarakham</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Lip repair</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>2005</td>
<td>Khon Kaen</td>
<td>Airway difficulty, micrognathia with left unilateral cleft lip</td>
<td>Tracheostomy and distraction osteogenesis Palatoplasty</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>2005</td>
<td>Khon Kaen</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Palatoplasty</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>2006</td>
<td>Udon Thani</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Distraction osteogenesis Palatoplasty</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>2006</td>
<td>Sakon Nakhon</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Palatoplasty with bilateral myringotomy</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>2009</td>
<td>Roi Et</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Feeding program</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>2010</td>
<td>Maha Sarakham</td>
<td>Airway difficulty, micrognathia with cleft palate</td>
<td>Palatoplasty with bilateral myringotomy</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>2010</td>
<td>Loei</td>
<td>Airway difficulty, micrognathia with cleft palate, hypothyroidism, iron deficiency anemia</td>
<td>Palatoplasty with bilateral myringotomy</td>
</tr>
</tbody>
</table>

severe respiratory difficulty, micrognathia and cleft palate. Positioning was used successfully for management of the difficult airway then palatoplasty performed. She was lost to follow-up 3 weeks after the palatoplasty.

**Patient No. 10**

A male patient, born in 2005 in Khon Kaen province, presented with severe upper airway difficulty, micrognathia and cleft palate. Muscular VSD was an associated anomaly. Tracheostomy had been previously performed. Mandibular distraction osteogenesis was performed at the age of 41 days with subsequent distraction of 2.5 mm/day. The tracheostomy tube was removed 39 days after insertion of the distraction device. Palatoplasty with intravelarveloplasty was performed at the age of 1 year and 3 months. He had bilateral conductive hearing loss at the age of 1 year and 4 months and global delayed development (according to the Denver II at 19 months). Assessment of speech and language development also revealed that he had delayed speech and language development at 2 years and 4 months. Speech and language therapy were provided. He still had delayed speech and language development at 4 years old. At the last follow-up in 2011 at the age of 6 years, he had proper catch-up with mandibular growth.

**Patient No. 12**

A female patient, born in 2006 in Sakon Nakhon
province, presented with small mandible, tachypnea, stridor and cleft palate. Subsequent pneumonia requiring prolonged intubation developed. Mandibular distraction osteogenesis was performed at the age of 3 months and palatoplasty at the age of 17 months. At the last follow-up in 2011 at the age of 3 years and 9 months, she had proper catch-up with mandibular growth and was on a speech management program.

**Patient No. 13**

A female patient, born in Roi Et province in 2009, presented with moderate airway obstruction, micrognathia with a U-shaped cleft palate. Positioning was used successfully for management of the difficult airway. She had bilateral conductive hearing loss that was found at 6 months. Medication treatment for middle ear pathology was not successful, bilateral myringotomy and palatoplasty which was performed at aged 11 months. At the last follow-up at 2 years old in 2011, she had normal speech and language development with proper catch-up and mandibular growth.

**Patient No. 14**

A female patient, born in Maha Sarakham province in 2010, presented with moderate airway obstruction, micrognathia with a U-shaped cleft palate.

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**Fig. 3**

Patient No. 10 presented with severe respiratory difficulty, micrognathia with cleft palate and tracheostomy (upper row). Plain films of skull, AP and lateral view (lower row), show a severely hypoplastic mandible.

**Fig. 4**

Intraoperative photos of patient No. 10 showing mandibular distraction device and its placement.

**Fig. 5**

Perioperative photos of patient No. 10 during insertion of device, after its removal and of the tracheostomy.

**Fig. 6**

Patient No. 10 at 6 years of age. Photos (upper row) and skull radiology (lower row) show proper catch-up with mandibular growth.

**Fig. 7**

Intra-operative photos of patient No. 12 showing small mandible.
She was managed successfully with conservative management and a feeding program.

She passed the hearing screening for at risk infants at 3 months using Transient Acoustic Emission (TEOAEs) and bilateral normal hearing which was followed up at 6 months using TEOAEs and behavioral observational audiometry.

**Patient No. 15**
A female patient, born in 2010 in Loei province, was referred with severe respiratory difficulty, micrognathia with a cleft palate, subclinical hypothyroidism and iron deficiency anemia, which was treated by tracheostomy, external device for mandibular distraction osteogenesis, palatoplasty and bilateral myringotomy. Photos at the last follow-up at the age 1 year 3 months are shown.
Subsequent pneumonia and sepsis with prolonged intubation developed. A tracheostomy and external device mandibular distraction osteogenesis were performed at the age of 3 months with subsequent distraction 2 mm/day. Palatoplasty with bilateral myringotomy was performed at the age of 11 months. The tracheostomy was removed at the age of 1 year due to a subglottic stenosis. After removing the tracheostomy, the patient continued to have difficulty swallowing and needed to be fed via an orogastric tube. Aspiration occurred so she was given a swallowing program by a speech and language pathologist. She still had difficulty breathing and with aspiration so a secondary tracheostomy was performed. Oronasal feeding tube and swallowing train were continued for dysphagia treatment. She had delayed speech and language development, especially expressive modality.

Discussion

PRS is pathogenically heterogeneous with nearly half of the patients having an underlying syndrome (the most common being Stickler syndrome). Developmental delays are more likely present in syndromic patients\(^{(10)}\). The challenges for management for patients with PRS are management of upper airway obstruction from glossoptosis or repositioning of the tongue. Additionally, patients with the most severe manifestations and life-threatening respiratory compromise may also have impairment of their feeding ability, especially while eating, due to glossoptosis which causes obstruction of the upper airway and results in poor nutrition and failure to thrive. Four types of airway obstruction may present in patients with PRS including (a) posterior movement of the tongue to the pharyngeal wall (b) the tongue compressing the soft palate into the posterior pharyngeal wall (c) lateral pharyngeal wall moving medially and (d) the pharynx constricting in a circular manner. The use of nasoendoscope may be helpful to evaluate the trachea and oropharynx\(^{(11)}\).

Radiographic evaluation consist of plain film of skull and/or CT scan may be used to demonstrate a symmetrical hypoplasia of the mandible with or without condylar and coronoid hypoplasia, and a lateral radiograph of the soft tissues of the neck and also be used to detect glossoptosis\(^{(12)}\).

For primary management of airway insufficiency in patients with PRS, some recommended protocols had been advocated, including being in a prone position with or without nasopharyngeal airway, prolonged intubation, tongue-lip adhesion, mandibular distraction osteogenesis, and tracheostomy. Conservative management for airway insufficiency in patients with PRS can often be effectively performed with prone positioning and cervical extension\(^{(13)}\), which is recommended for infants demonstrating improvement in weight gain, strength and tongue coordination. The prone positioning may be used for 1 to 6 months to allow adaptation and subsequent mandibular growth. If the positioning fails, the nasopharyngeal airway may be used with nasogastric tube feedings. As the patient with PRS grows, mandibular growth catches up in most of them and they will no longer have airway insufficiency. Most of non-syndromic PRS patients are successfully managed with conservative therapy; However, the treatment modality depends upon many factors, such as the extent and severity of oxygen desaturation during sleep, and failure to thrive\(^{(6)}\). Conservative management in a prone position plus a feeding program was successful in 12 of 15 patients in the present study.

Operative intervention to manage airway insufficiency is indicated in patients with PRS who (a) fail (or are likely to fail) the non-operative treatment (b) do not have adequate oropharyngeal adaptation (c) suffer from failure to thrive and inability to control tongue movement or (d) cannot be successfully extubated. The options for surgical treatment include tongue lip adhesion\(^{(14)}\) or tracheostomy\(^{(17)}\). Tongue lip adhesion benefits the patient with PRS who does not respond to conservative treatment as well as benefitting most of those who have this type of obstruction with posterior movement of the tongue to the pharyngeal wall\(^{(13)}\). Notwithstanding, the long-term complications may include developmental delays and articulation deficits\(^{(16)}\).

Kaban et al described the specific criteria for surgical intervention, including respiratory rate > 60 min, FiO2 requirement > 60%, PaO2 < 65 mmHg, PaCO2 > 60 mmHg, weight gain < 100 g/week and SaO2 < 70%\(^{(17)}\). Traditionally, tracheostomy has been the most effective and definitive option for immediately relieving severe upper airway obstruction in patients with PRS\(^{(18)}\). However, it may be associated with frequent morbidity, including swallowing dysfunction, delay in speech and language development problems\(^{(19,20)}\), high cost, a mortality rate of 1-4%\(^{(21,22)}\) and late decannulations, which may last several years and produce a significant negative psychological impact on the patient's family\(^{(23)}\). Feeding difficulties are common in patients with PRS and feeding methods to address this problem
may include upright feeding techniques, modification of the nipple for bottle feeding, temporary use of a naso- or orogastric feeding tube and placement of a gastrostomy, in more severe case\(^6,24\).

Mandibular distraction osteogenesis was first described for treating patients with hemifacial microsomia by McCarthy et al in 1992\(^{25}\). It has been used subsequently to manage patients with respiratory insufficiency from micrognathia or retrognathia\(^{20}\) and is a treatment option in patients with PRS\(^{27}\). The mechanism of gradually lengthening the mandible can correct the posterior tongue base position and relieve the upper airway obstruction. Mandibular distraction osteogenesis of the mandible has been successfully used for treatment of patients with PRS and in three patients in the current study. Many recent studies reported mandibular advancement during the first few days of life\(^{28,29}\).

Mandibular distraction osteogenesis is performed by (a) making a mucosal and submandibular incision (b) applying distraction pins to the mandible (c) an osteotomy to the buccal and superior cortical bone and lingual cortical bone, taking care to avoid injury to the inferior alveolar nerve and tooth buds and (d) applying the device to the pins on either side of the mandible. In infants with PRS, the distraction may be performed 2 to 3 mm per day\(^{30}\). Over a 6-year period, Singhal and Hill reported the use of mandibular distraction osteogenesis in 50 neonates with PRS. All of the patients were able to feed entirely by mouth within 2 weeks and thereafter had appropriate weight gain. Moreover the tracheostomy could be removed in 48 patients\(^{31}\). The majority of patients with PRS treated with mandibular distraction were able to avoid tracheostomies or successfully underwent decannulated tracheostomies (i.e., compare our patients No. 10, 12 and 15).

Currently, there are two main types of distraction devices: external and internal. The advantages of an external device are (a) the multidirectional vectors that can be applied during the distraction phase and (b) the ability to perform multiplanar distraction to accommodate mandibular asymmetries. The disadvantages are (a) the greater risk to the marginal mandibular branch of the facial nerve and (b) scarring at the external pin sites\(^{32}\). The advantages of internal devices are (a) no need for a cumbersome external device and (b) no risk of pin-associated scar formation or infection. The disadvantages are (a) the unidirectional or linear vector of movement and (b) the requirement of a second general anesthetic for removal of the device.

Many different imaging modalities have been used for pre- and post-operative assessments of mandibular distraction osteogenesis in patients with PRS including radiographs (Fig. 2, 6 and 8) and a 3-D CT scan to demonstrate the ramus and body of the deficient mandible allow proper planning of the osteotomies and distraction vectors\(^{33,34}\) and locating the position of the tooth buds and the inferior alveolar nerve.

**Conclusion**

The challenges in the management of patients with PRS in Thailand and other developing countries are the evaluation and management of airway insufficiency and feeding difficulty. Interdisciplinary team management comprising a plastic surgeon, a pediatrician experienced in neonatal respiratory medicine, a pediatric anesthesiologist, a speech and language pathologist, other health professionals and nurse co-ordinator is important for ensuring proper evaluation, improved care and optimum outcomes. Options and different modalities for the management of airway insufficiency and feeding difficulties should be considered according to patient’s evaluation and response to treatment. Mandibular distraction osteogenesis has been increasingly used to manage patients with respiratory insufficiency and it is a treatment option for patients with PRS.

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**Potential conflicts of interest**

None.

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ปิแอรโรแบงซีเควนซ์: ความท้าทายด้านการประเมินการรักษาและบทบาทของการยืดถ่างขยายกระดูกในระยะแรก

ปิแอรโรแบงซีเควนซ์: ความท้าทายด้านการประเมินการรักษาและบทบาทของการยืดถ่างขยายกระดูกในระยะแรก

ภูมิหลัง: ความท้าทายของการดูแลผู้ป่วยปิแอรโรแบงซีเควนซ์ คือ การประเมินและรักษาภาวะอุดกั้นทางเดินหายใจที่เกิดจากการยื่นหูของผู้ป่วยและการทำความสะอาดภายในลำคอวัสดุและวิธีการ: การศึกษาเป็นการทบทวนบันทึกทางการแพทย์ของผู้ป่วยปิแอรโรแบงซีเควนซ์ที่ได้รับการรักษาโดยผู้นิพนธ์ในโรงพยาบาลศรีนครินท์ในระหว่างปี พ.ศ. 2544-2554

ผลการศึกษา: มีผู้ป่วยปิแอรโรแบงซีเควนซ์ที่ได้รับการรักษาโดยผู้นิพนธ์จำนวน 15 ราย เป็นเพศชายต่อเพศหญิงอัตรา 1.8 ต่อ 1 ผู้ป่วยทุกรายถูกตรวจวินิจฉัยการยืดถ่างขากรรไกรและลิ้นตกไปด้านหลัง การรักษานานทางเดินหายใจยาวนาน ผู้ป่วยราย 1 รายมีอาการอุดกั้นทางเดินหายใจรุนแรง จึงต้องการเจาะลำคอ 3 ราย เมื่อมีการเจาะลำคอ การเจาะลำคอสำเร็จ 12 ราย ผู้ป่วยราย 3 ราย ที่ได้รับการเจาะลำคอ 1 รายมีอาการลิ้นที่มีการเจาะลำคอ 2 ราย

สรุป: การรักษาภาวะอุดกั้นทางเดินหายใจและช่วยการให้อาหารมีวิธีการทำได้โดยการจัดท่ากึ่งนอนคว่ำอย่างเหมาะสม การเจาะลำคออาจช่วยลดการอุดกั้นทางเดินหายใจ การเจาะลำคอที่เหมาะสมจะช่วยให้การรักษาดีขึ้น