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Review

Pierre Robin Sequence, from conception to realization

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ABSTRACT

Pierre Robin Sequence (PRS) comprises a combination of craniofacial defects, including micro/retrognathia, glossoptosis, and respiratory obstruction. Cleft palate is often associated with PRS, however it is not required for diagnosis. The diagnostic criteria for PRS is poorly defined with a large variation in phenotypic presentation. Multiple theories exist regarding the etiology and pathogenesis of PRS, including mechanical, neurological maturation, and rhombencephalic dysneurulation. PRS can be classified into isolated PRS, syndromic PRS, and associated PRS. Defining the classification can aid in determining a treatment plan. Management is largely dependent upon the infant's phenotypic presentation and may require respiratory support with possible surgical intervention to maintain airway patency. Implications for the caregiver focus on identifying the PRS phenotype, obtaining a thorough prenatal history, developing a multidisciplinary approach to care, and ensuring growth and development are supported. Through thorough management positive outcomes are achievable in the infant with PRS.

Pierre Robin Sequence (PRS) is considered a heterogeneous condition, in which there is no single cause for the disorder. Reports of the PRS phenotype have been recorded as early as the 19th century. While this disorder has been seen for almost two centuries, little is truly known about this condition and why it occurs. Known facts and hypotheses regarding this condition will be discussed, including its definition and incidence rate, theories of pathogenesis, phenotype and natural history, clinical management, recurrence rates, and implications for the care provider.

1. Definition of the disease and incidence

According to the Pierre Robin Sequence (PRS) Foundation, PRS is a congenital condition in which infants are born with a triad of craniofacial abnormalities, including a "smaller-than-normal lower jaw (micrognathia) or set back from the upper jaw (retrognathia), a tongue that falls back in the throat and obstructs the airway (glossoptosis), and difficulty breathing" (PRSF, n.d., para 1). A forth characteristic that is commonly seen but not required for diagnosis includes a cleft palate, an abnormal opening in the roof of the mouth (PRSF, n.d., para 1). The cleft palate may include either the hard or soft palate and may be described as being U shaped or V shaped. As a result of varying diagnostic criteria, reported incidence rates range from 1:8,500 to 1:14,500 (Tan et al., 2013). Mortality rates over the past ten years for infants with PRS is estimated to be 1.7%–11.3% and as high as 26% for children with multiple malformations (Evans et al., 2011; Paes et al., 2013).

PRS was named after a French physician who first published the combination of abnormalities in 1923 (Tan et al., 2013). While Pierre Robin is largely known for classifying this disorder, the triad of anomalies was first documented by St. Hilaire in 1822, followed by Fairban in 1846 and by Shukowsky in 1911 (Evans et al., 2011). This combination of defects has historically acquired several associated names, including Robin Sequence, Robin Syndrome, Robin Complex, Robin anomalad, and Pierre Robin Syndrome (NIH, 2016a,b). The term syndrome has since been "reserved for those errors of morphogenesis with the simultaneous presence of multiple anomalies caused by a single etiology" (Tewfik et al., 2017, para 1). The term sequence has since been accepted, referring to one abnormal feature leading to a sequence of events in utero causing additional abnormalities (NIH, 2016a,b).

Classification for PRS has been further defined as being isolated, syndromic, or associated. Isolated PRS accounts for approximately half of the total cases, consisting solely of the associated PRS defects (Lind et al., 2015). Isolated PRS is frequently seen in new (de novo) genetic changes without an associated family history (NIH, 2016a,b). Syndromic PRS (sPRS) refers to the PRS phenotype as part of an associated syndrome. Evans el at. (2011) noted that more than 40 syndromes have been identified as having phenotypic PRS presentation. According to the National Organization for Rare Disorders (2004), Stickler syndrome, 22q11.2 deletion syndrome, Treacher Collins syndrome, and cerebro-costo-mandibular syndrome are commonly associated genetic disorders with PRS. Stickler Syndrome, a connective tissue disorder, being the most prevalent and is identified in 11–18% of individuals with PRS (Evans et al., 2011). Lastly, associated PRS (aPRS) refers to individuals with the PRS phenotype with associated defects that are unable to be categorized as a syndrome (Lind et al., 2015).

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2. Etiology and pathogenesis

The specific cause of PRS is unknown, however multiple theories exist hypothesizing its pathogenesis. The most widely accepted theory is the mechanical theory. This theory focuses on the initial development of mandibular hypoplasia as a result of both intrinsic and extrinsic factors. The mandible is formed from the first branchial arch. Disruption in the outgrowth process of the mandible typically occurs between the seventh and 11th weeks of gestation (Tewfik et al., 2017). As a result of this hypoplasia and failed mandibular outgrowth, the oropharyngeal space is reduced. This reduced oropharyngeal space results in the tongue being held high and upward with posterior displacement. The obstruction generated by tongue displacement inhibits the paired palatal shelves from fusing (Evans et al., 2011). This theory is highly accepted as it explains the development of the commonly seen cleft palate without an associated cleft lip (Tan et al., 2013).

Numerous associated gene mutations have been identified to intrinsically interfere with mandibular development, including COL2A1, COL11 A1, COL11 A2, IGBP1, and SOX9 (Chiriac et al., 2008). Gene mutations related to PRS may include deletions or translocations. The National Institute of Health (NIH) has identified that genetic changes near the SOX9 gene, located on chromosome 17 (17q24), are the most commonly seen genetic mutation linked to PRS (NIH, 2016a,b). This gene plays a critical role during embryonic development on skeletal development and sex determination (NIH, 2016a,b). When disruption occurs to the enhancer regions that regulate the SOX9 gene, reduced SOX9 protein production occurs which has been connected to impaired mandibular outgrowth (NIH, 2016a,b).

Extrinsic factors, such as intrauterine impairment, have been frequently reported in infants with PRS. Oligohydramnios, resulting in intrauterine growth restriction, has been seen to restrict mandibular growth in animal studies (Evans et al., 2011). The physical compression created as a result of oligohydramnios leads to compression on the mandible contributing to cleft palate development. Generalized intrauterine impairment, as seen with fetal alcohol syndrome, can include the PRS phenotype (Printzlau and Andersen, 2004).

A second theory that exists is the neurological maturation theory. This theory implies that a delay in neurological maturation has been associated with musculature development of the tongue, the pharyngeal pillars and the palate, as well as a delay in hypoglossal nerve conduction (Chiriac et al., 2008). The spontaneous mandibular growth often seen within the first year of life supports this theory. The third published theory includes the rhombencephalic dysneurulation theory. This theory suggests that disorganized motor regulation within the hindbrain results in major complications with anatomical development, ontogenesis (Chiriac et al., 2008).

3. Phenotype and natural history

The degree of phenotypic presentation in infants with PRS varies greatly. As previously mentioned, the diagnostic criteria used for PRS has been historically poorly defined with no known gold standard, as the severity of symptoms have considerable variation. The triad of craniofacial abnormalities, consisting of micro/retrognathia, glossoptosis, and respiratory obstruction, presents with differing levels of severity. A classification system has been developed by Cole et al. (2008) that has shown to clarify treatment pathways while enhancing communication amongst the multidisciplinary team. This classification system consists of three grades and includes cleft palate as a diagnostic factor. Additionally, the infants feeding capabilities are taken into consideration with this grading system, as feeding challenges are highly associated with the degree of micro/retrognathia. Grade one includes infants with a satisfactory feeding assessment without signs of respiratory distress. Grade two includes infants whose feeding precipitates respiratory distress needing a feeding tube, having consistent glossoptosis, and include infants with failure to thrive. Grade three includes infants who are unable to feed orally as a result of moderate to severe respiratory distress requiring a form of additional airway support and have consistent glossoptosis (Cole et al., 2008). While this classification system is not universally practiced, it does help to offer clinical clarification with consistent guidance of treatment.

Tan et al. (2016) identified that the observed respiratory distress and feeding complications frequently seen postnatally occur predominantly secondary to congenital structural abnormalities, such as micrognathia/retrognathia and glossoptosis. Differentiating between micrognathia and retrognathia can help guide clinical management. Micrognathia refers to a disproportionately small jaw with decreased bone mass. Retrognathia refers to a normal sized jaw with normal bone mass that is posteriorly positioned. Increased severity of respiratory distress has been identified with micrognathia whereas retrognathia is associated with no to minimal respiratory distress (Tolarova, 2016).

As previously mentioned, cleft palates are a commonly seen phenotypic feature of infants with PRS, as micrognathia and glossoptosis can alter the palates development in utero. Cleft palate occurs in approximately 90% of infants with PRS (Evans et al., 2011). While cleft palates are difficult to diagnose prenatally due to visualization limitations with US, dental anomalies may be an additional prenatal marker for the cleft sub-phenotype (Lind et al., 2015; Tan et al., 2013). Dental anomalies, such as hypodontia are approximated to be 50% more prevalent in infants that have cleft palate associated PRS than infants with PRS without cleft palate (Tan et al., 2013). Additionally, infants with PRS with a cleft palate are at risk for conductive hearing loss related to frequent ear infections secondary to fluid accumulation associated with a cleft palate (Tan et al., 2013).

4. Management

As a result of the varying severity of the PRS phenotype, clinical management can be inconsistent (Cole et al., 2008). Commonly associated medical problem seen with PRS include respiratory obstruction/respiratory distress, feeding difficulties and failure to thrive (Rathé et al., 2015). Depending on the severity of micro/retrognathia, the respiratory management of these infants can be very complex and challenging. Methods for airway management with PRS includes the following: supportive prone positioning, use of a nasopharyngeal airway (NPA), extended endotracheal intubation, and surgical interventions such as tracheostomy, mandibular distraction osteogenesis, and glossopexy (Rathé et al., 2015).

While most cases of PRS can be treated through a conservative approach to airway obstruction, such as prone positioning and/or a NPA, an approximated 23% will required surgical intervention as a result of major airway obstruction (Paes et al., 2013). Glossopexy, refers to a tongue lip adhesion procedure where the tongue is attached to the lower lip, resulting in anterior placement of the tongue and relief of airway obstruction. Potential complications for glossopexy include tongue and lip scarring, as well as infection (Viezel-Mathieu et al., 2016). Tracheostomy can be used as both a temporary and long-term airway, bypassing the airway obstruction caused by micrognathia. Potential complications for tracheostomy include accidental decannulation, laryngeal/tracheal stenosis, speech delay (Paes et al., 2013). Mandibular distraction osteogenesis is a method of lengthening the mandible, creating new bone growth achieved through the use of a distractor surgically placed within the jaw bone. Complications related to this procedure include infection, with the potential for a second surgical intervention if non-absorbing distractors are used (Murage et al., 2014; Paes et al., 2013). Choice of surgical intervention is dependent upon the medical team and specific to the individual with PRS.

Feeding complications and failure to thrive may appear secondary to respiratory insufficiency in infants with PRS, however “they can also be due to swallowing dysfunction, aspiration, and gastro-esophageal reflux disease (GERD)” (Rathé et al., 2015, p. 1207). Cleft palates impair the infant's ability to produce a negative pressure necessary for

creating a functional suck (Rathé et al., 2015). Early consultation with occupational therapy and speech therapy will help to establish an appropriate feeding plan to optimize results. A palatal plate may be used in infants with a cleft palate, to help provide a seal to generate an effective suck. Additionally, the small jaw seen with PRS alters the infant's ability to contract the lip muscles (orbicularis oris muscle) contributing to bottle and breast-feeding challenges (Rathé et al., 2015). A special needs feeder may be necessary to support the infants feeding challenges. In more severe cases of PRS, oral feeding may not be feasible due to anatomy and/or respiratory distress. Nasogastric (NG) tube feedings may be appropriate or even gastrostomy tube (GT) placement for anticipated extended feeding use (Rathé et al., 2015).

Additional workup and management for patients with PRS should include a full genetic evaluation to confirm diagnosis and evaluate for any associated syndromes. With Stickler syndrome being commonly associated with PRS, an ophthalmology consultation should be obtained (Evans et al., 2011). Stickler Syndrome is the leading cause of blindness and retinal detachment in children and early prophylactic screening is necessary (Evans et al., 2011). In both sPRS and aPRS, additional workup and evaluation should be performed guided by the specific associated syndrome or anomalies (Evans et al., 2011).

5. Recurrence risk and genetic counseling

The recurrence risk associated with PRS is dependent upon its classification of being isolated, syndromic, or associated. Isolated PRS is typically not inherited and is a result of new (de novo) genetic changes, occurring in individuals with no familial history of the disorder (NIH, 2016a,b). Syndromic PRS follows the same inheritance pattern of the specific syndrome it is associated with. When this disorder is inherited, typically following an autosomal dominance pattern, there will be a 50% chance of passing the disorder to their offspring, equally affecting both males and females (NIH, 2016a,b).

Early involvement of a geneticist can be helpful in an accurate diagnosis of PRS and may contribute to an appropriate plan of care. Chromosomal analysis should be performed, including a FISH for 22q11 deletion as well as DNA testing for collagen genes mutations, indicating concerns for stickler syndrome. Additionally, genetic consultation and counseling is beneficial to help families understand the recurrence risks related to PRS. While ultrasonography is an unreliable diagnostic tool, future pregnancies should have a level II ultrasound (US) to assess for identifiable PRS features (Lind et al., 2015).

6. Implications for providers

In it important for the care providers to be familiar with phenotypic features of PRS, as prenatal US diagnosis in uncommon. Prenatal diagnosis is observed in 7%–22% of the PRS population (Lind et al., 2015). Micro/retrognathia, glossoptosis, and cleft palate are difficult to define on prenatal US. Lind et al. (2015) performed a retrospective analysis on the outcomes of infants who were identified to have PRS features on US. This study found that the association of retrognathia with cleft palate resulted in a predictive value of 100% for infants with PRS. Additionally, regardless of phenotypic PRS features on US, severity of presentation was unpredictable (Lind et al., 2015). The results of this study therefore imply that if indeed report is received indicating any of the phenotypic features of PRS, the medical and nursing team should be prepared to manage the most severe classification, as there are no known prenatal indicators for severity.

Upon diagnosis or expressed concern for PRS in an infant, the providers should obtain a thorough prenatal history. “Detailed prenatal history can highlight extrinsic causes of PRS such as foetal constraint, oligohydramnios, or teratogenic exposure” (Tan et al., 2013, p. 301). It is also important to determine the classification of PRS, as isolated, syndromic, or associated. Upon clarification, a more tailored plan of care can be created and an individualized multidisciplinary team can be shaped to treat additional related defects.

With the associated feeding challenges seem in PRS, the provider may consider optimizing caloric intake; supporting the consumption of smaller feeding volumes, while decreasing the amount of time feeding. This practice can promote energy conservation and promote growth (Evans et al., 2011). The care providers should also take into consideration the increased risk for aspiration and GERD with PRS, incorporating occupational therapy and speech therapy early. If a cleft palate is present, consultation with and referral to a cleft palate clinic is optimal if available. The provider should also ensure appropriate screening for obstructive sleep apnea, to minimize developmental delays associated with recurrent hypoxia (Evans et al., 2011). After infancy, the care providers should focus their management on the child's growth, speech, and cognitive development (Evans et al., 2011).

7. Conclusion

In conclusion, the heterogeneous nature of PRS contributes to its unclear diagnostic criteria, making a consistent and uniform approach to care challenging and unrealistic. Infants with PRS need an individualized approach to care, unique to their specific phenotype. Clinical management of infants with PRS is multifaceted, requiring the potential for complex airway management. Emphasis needs to be placed on optimizing growth and nutrition, while supporting cognitive development. With a cohesive multidisciplinary approach to care, a good prognosis is achievable (Evans et al., 2011).

Ethical approval

Ethical approval was not required.

Conflicts of interest

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Appendix A. Supplementary data

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