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Pierre Robin Syndrome: A Literature Review

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Abstract

Introduction: Stomatologist Pierre Robin first described this syndrome in 1923 as a triad of micrognathia (small and symmetrically receding mandible), glossoptosis (tongue obstructing the posterior pharyngeal space), and upper airway obstruction. The aim of the present systematic literature review is to describe relevant information for the proper diagnosis and treatment of Pierre Robin Syndrome.

Materials and Methods: A search for scientific articles was performed in the following databases: PubMed, Scielo, SpringerLink, Wiley Online Library, Science Direct, and Virtual Health Library. The search included articles published since 2012, in English and Spanish. Each of the selected articles was analyzed in an exhaustive manner.

Keywords: Pierre Robin Syndrome; Multidisciplinary Treatment; Diagnosis; Respiratory Condition; Dental Malocclusion

1. Introduction

Stomatologist Pierre Robin first described this syndrome in 1923 as a triad of micrognathia (small and symmetrically receding mandible), glossoptosis (tongue obstructing the posterior pharyngeal space), and upper airway obstruction. This heterogeneous entity can present in isolation as a non-syndromic Pierre Robin or in association with other syndromes, for example, feeding disorders, pulmonary events due to broncho-aspiration, gastroesophageal reflux, which is associated with mortality rates due to respiratory obstruction in newborns (1)(2)(3).

The diagnosis and initial patient management with Pierre Robin Syndrome (PRS) often take a multidisciplinary approach. A comprehensive assessment may require the involvement of specialties such as maternal-fetal medicine, genetics, neonatology, pulmonary and sleep medicine, developmental pediatrics, plastic surgery, oral surgery, orthodontics, dentistry, otolaryngology, ophthalmology, pediatric surgery, cardiology, speech pathology, feeding specialists, audiology and neurology. (4) Thus, treatment should ensure permanent airway clearance so that respiratory and feeding problems are eliminated.

The aim of the present systematic literature review is to describe relevant information for the proper diagnosis and treatment of Pierre Robin Syndrome.

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2. Material and methods

A search for scientific articles was performed in the following databases: PubMed, Scielo, SpringerLink, Wiley Online Library, Science Direct, and Virtual Health Library. The keywords were selected taking into account the Medical Subject Headings (MeSH) and the Health Sciences Descriptors (DeCS), for a more selective search based on the study, the Boolean operators AND, OR, and NOT were used, thus the terms selected for the search were: Pierre Robin Syndrome, multidisciplinary treatment, diagnosis, respiratory condition, and dental malocclusion. The search included articles published since 2012, in English and Spanish. Each of the selected articles was analyzed in an exhaustive manner.

2.1. Theoretical framework

PRS is defined as an alteration during embryonic development of the first branchial arch in the first nine weeks of gestation thus originating a hypoplastic mandible with posterior insertion of the tongue preventing the closure of the distal palate which consequently prevents a correct development of the cranio-encephalic mass (5). Traditionally, Pierre Robin Syndrome has been described from the triad of micrognathia, glossoptosis, and upper airway obstruction (1, 2).

2.1.1. Etiology

The etiology of Pierre Robin Syndrome is typically separated into isolated and syndromic PRS. Isolated or also known as non-syndromic PRS is related to mutations on chromosomes 2, 4, 11, or 17. Some evidence has indicated that SOX9 or KCNJ2 mutations (on chromosome 17) may affect the development of facial structures and cartilage, leading to PRS. On the other hand, there is syndromic PRS, which represents 60% of PRS. There have been 34 syndromes associated with syndromic PRS, the most common being Stickler syndrome, defined as a mutation of the COL genes, which affects collagen formation (6).

2.1.2. Pathophysiology

Considering the pathogenesis of the disease, 3 main theories have been proposed: mechanical theory, neurological maturation theory, and jaw compression theory (3).

- Mechanical theory: This is the most accepted theory. The initial event, mandibular hypoplasia, occurs between the 7th and 11th week of gestation. This keeps the tongue high in the oral cavity, causing a cleft palate and preventing the palatal pillars from closing. This theory explains the classic inverted U-shaped cleft and the absence of an associated cleft lip. Oligohydramnios may play a role in the etiology, as the lack of amniotic fluid may cause the deformation of the chin and subsequent impaction of the tongue between the palatal pillars (7).
- Neurological maturation theory: It explains that there is a neuromuscular delay in the musculature of the tongue, pharyngeal pillars, and palate. The delay has been observed in the electromyogram. In this situation, the tongue does not stimulate mandibular growth or fusion of the palatal shelves. As a consequence, micrognathia and difficulty breathing may occur (8).
- Mandibular compression theory: Mandibular growth may be restricted by multigravida pregnancy, oligohydramnios, or uterine anomalies. All of these conditions limit the normal range of extension of the flexed fetal head. For this reason, the fetal chin is compressed over the sternum, and mandibular growth is restricted. This restricted mandibular growth inhibits downward and forward movement of the tongue, thus preventing elevation and fusion of the palatal surfaces. Thus, micrognathia, cleft palate, and narrowing of the airway are the main consequences (8).

2.1.3. Diagnosis

Diagnosis is based on the signs and symptoms found in patients, in addition to imaging tests. The main imaging techniques used are panoramic radiography associated with cephalometry and computed tomography, photographic documentation, or computer image acquisition and manipulation techniques. Currently, the use of polysomnography has been highlighted to identify causes of apnea, as well as to document the degree of obstruction (8).

- *Micrognathia:* Micrognathia is a medical sign present in approximately 91% of people affected by PRS (10). It is a reduced mandibular size that causes upward and backward displacement of the tongue, preventing the closure of the palatal shelves before the 10th week of gestation (4, 11,12). In prenatal diagnosis, it is important to evaluate the second-trimester micrognathia and the subsequent tongue posture, which can be defined as an indirect sign of cleft palate (13).

- *Glossoptosis:* Glossoptosis is key to the diagnosis of PRS, defined by the displacement of the base of the tongue into the oropharynx and hypopharynx (8). The tongue causes obstruction of the posterior pharyngeal space and upper airway, with consequent breathing and feeding difficulties that are more frequent and more severe in the neonatal period (1,11,13). Nasal-pharyngeal laryngoscopy can be useful to show the position of the tongue in relation to the oral cavity and oropharynx (8). In addition, endoscopy and computed tomography (CT) can also be useful to quantify the level of obstruction (6). This sign is seen in approximately 70-85% of diagnosed cases (10).
- *Cleft palate:* The classic triad of PRS is mainly associated with a U-shaped cleft palate, although a V-shaped cleft palate has also been found (6,8,13). There is debate as to whether cleft palate is a mandatory Robin Sequence feature (1), however, 85% of these patients have a concomitant cleft (4,14,15). After diagnosis, the type of cleft should be classified by identifying the shape, size, and extent, to predict its influence on airway obstruction and subsequent tongue development (8).
- *Respiratory dysfunction:* Although glossoptosis is probably the main cause of respiratory problems, in patients with PRS, ventilatory dynamics are influenced by many factors. Recognition, characterization, and treatment of these problems are critical to promote proper development and avoid more severe comorbidities. Children with PRS show variable respiratory problems: mild dysfunction, apnea, increased respiratory muscle activity, cyanosis, or respiratory failure. Clinically, patients may present with frequent desaturation, abnormal breath sounds, neurological sequelae, and hypoxia up to the development of "cor pulmonare". Sleep-related ventilation disorders are due to the collapse of the pharyngeal muscles and high resistance to airflow through the upper airways (8).
- *Hypodontia:* The prevalence of hypodontia in children with isolated cleft palate is reported to be four to five times higher than in children without cleft palate and is higher in the mandible than in the maxilla. The prevalence of dental agenesis, excluding third molars, ranges from 31.5% to 50%, with a trend toward a higher frequency of hypodontia as cleft severity increases. In children with PRS, congenital missing teeth are more common in the mandible than in the maxilla (16).

2.1.4. Classification of Pierre Robin Syndrome

The quickest and most common classification distinguishes Pierre Robin Syndrome as isolated or syndromic. But classification can also be considered in relation to the *severity of symptoms*, Couly made the first real classification of PRS in 1988, later revised by Caouette-Laberge in 1994. Patients were evaluated for respiratory and nutritional problems. More recently Cole et al. have performed a retrospective analysis in children with Pierre Robin Syndrome and have determined a new classification in relation to clinical signs and therapeutic treatment, distinguishing patients into three different grades of severity (6,8,9).

- Grade 1, less severe: micrognathia, cleft palate, and mild glossoptosis. Minimal respiratory dysfunction and satisfactory nutrition (8).
- Grade 2, moderate: micrognathia, cleft palate, and medium-grade glossoptosis. Upper airway obstruction has a discontinuous pattern, defined mainly by classic inspiratory stridor, and worsens with feeding. Patients often require a nasogastric tube for some months to restore ventilation dynamics (8).
- Grade 3, more severe: micrognathia, severe glossoptosis, cleft palate, and moderate to severe upper airway obstruction. Continuous monitoring of oxygen saturation is required. Respiratory dysfunction and glossoptosis do not provide normal nutrition and the patient needs to be fed through a nasogastric tube (8).

Although Cole's classification is the most common, Li et al. determined the "Vancouver classification" for children affected by PRS. Based on their clinical experience, they proposed to distinguish patients into four grades of severity (from 0 to 3) in order to define a more precise algorithm for the choice of treatment (8).

- Grade 0: micrognathia and maxillomandibular discrepancy less than 10 mm, mild glossoptosis, no respiratory dysfunction, normal feeding. These patients respond optimally to non-surgical treatment and improve clinical conditions with a prone position (8).
- Grade 1 is characterized by: micrognathia and maxillomandibular discrepancy of less than 10 mm. There is a moderate or severe degree of glossoptosis and feeding difficulty requiring the use of a nasogastric tube. There is no respiratory disease, but oxygen desaturations can also be found in a prone position. In these cases, surgical repositioning of the tongue (tongue-lip adhesion) may be a good solution (8).
- Grade 2: micrognathia is more pronounced and the discrepancy between the maxilla and mandible is 10 mm. The severe degree of glossoptosis is associated with oxygen desaturation also in a prone position and difficulty in feeding requiring the use of a nasogastric tube. There are some alterations in ventilatory dynamics. The surgical treatment of choice is a mandibular osteogenic distraction (8).

- Grade 3: Micrognathia is severe and the airway is severely compromised. A tracheostomy is often required (8).

2.1.5. Treatment

Nonsurgical therapies

- Prone positioning: originally proposed by Robin, he hypothesized that the narrow pharyngeal space in the PRS can be corrected by moving the mandible forward by gravity in infants sleeping on their stomachs. In some case series, it was reported that 50-80% of patients received satisfactory treatment in a prone position alone. However, very few studies objectively documented the effectiveness of prone positioning. Given this apparent lack of efficacy, combined with the fact that the prone sleeping position is associated with a 14-fold increased risk of sudden infant death, prone positioning cannot currently be recommended as an intervention aimed at improving breathing in PRS infants (17).
- Nasopharyngeal airway: this device seeks to bridge the narrow pharyngeal space that characterizes PRS infants by inserting an endotracheal tube into one of the nares so that its tip is positioned immediately above the epiglottis (determined by endoscopy or radiographs). It should be noted that methods have been described to estimate the required length of the tube without the need for endoscopy or radiographs and to secure it securely to the nose. This treatment does not exert any stimulus on mandibular growth, nor does it encourage the tongue to assume a more desirable horizontal position. Therefore, while certainly valuable as a temporary measure, more data on long-term effectiveness are needed before recommending this approach as a routine treatment option in infants with PRS. (17)
- Tubinga Palatal Plate (TPP): Consists of a palatal base plate that covers the hard palate and cleft, as well as the alveolar ridges, and supports a single length (approximately 3 cm) velar extension (spur) ends just above the epiglottis and displaces the base of the tongue forward, thus opening the airway and correcting the underlying glossoptosis. The placement of the TPP is controlled by fiberoptic nasopharyngoscopy without sedation. It allows forward displacement of the base of the tongue to push the tongue far enough forward to erect the epiglottis, thus widening the pharyngeal space. The efficacy of PPT is determined periodically by sleep studies, the first being performed immediately prior to the start of treatment, and subsequently prior to discharge, and at least 3 and 6 months after starting treatment with PPT. The Mixed Obstructive Apnea Index (MOAI) in these studies should be less than three events/h; if it is more than three events/h, the angle or length of the velar extension is modified. Treatment is usually discontinued around 6-8 months of age, depending on the results of the sleep study (which should show a MOAI ≤ 1 event/h) and the facial profile at that time (17)

Surgical therapies.

When the grade is high and noninvasive treatments do not achieve the desired results, surgery becomes mandatory and should be performed as soon as possible (13).

- Tongue-lip attachment: Shukowsky, in 1902, developed a surgical technique to create an attachment of the tongue to the lower lip, taking the first step in the surgical treatment of airway obstruction due to glossoptosis (2). This is often employed in isolated PRS as a temporary measure while the mandible grows during the first years of life. Complications include lacerations, dehiscence, Wharton's duct injury, infection, and aspiration (6). Thus, it has not yet been demonstrated whether tongue-lip adhesion can be recommended as a good surgical approach for most children with PRS (17).
- Mandibular distraction osteogenesis: This is a surgical intervention that produces long-term results. This procedure advances and lengthens the mandible in 3 phases: latency, activation, and consolidation. Latency is the period of time after the osteotomy and before the distraction begins with the rotation of an external device that lengthens the distance between the bones at the fracture site. Consolidation is the time allowed for bone formation and healing at the osteotomy site (6). After a 48-h latency period, distraction proceeds at a rate of 2 mm/day at a rate of 0.5 mm four times a day. After 10 mm of distraction, the rate decreases to 1 mm/day at 0.5 mm twice daily until the patient has a class III occlusion. This overcorrection is considered necessary to maintain an adequate airway in the event of (partial) relapse after distraction. The devices are usually removed 4 to 8 weeks after the end of the distraction period. It is also possible to use a single-stage self-resorbable internal device (17). Complications include infection, osteomyelitis of the mandible, damage to the inferior alveolar nerve, bite deformities, and permanent teething loss (6). Surgery is strictly indicated when the distance is less than two millimeters or if oxygen saturation is less than 40% in a prone position (8).
- Tracheostomy: When distraction fails, the patient should undergo tracheostomy in order to ensure a patent and safe airway that facilitates swallowing without risk of aspiration or other complications arising from the baseline condition (2). As tracheostomy is associated with multiple morbidities, including laryngeal stenosis,

tracheomalacia, chronic pneumonia, and extensive nursing care, it is generally reserved for patients in whom no other intervention is considered a viable option. More recently, tracheostomy has been shown to be associated with higher financial costs compared to Osteogenic Mandibular Distraction. Despite these limitations, tracheostomy remains a life-saving intervention, especially for medically complex patients with multiple sites of airway obstruction (13,15,18).

3. Discussion

Gonzalez et al. describe that PRS is distinguished from other types of pathologies due to the presence of 3 fundamental clinical features which are cleft palate, glossoptosis, and micrognathia, they also mention that if left untreated these can lead to exhaustion, cardiac failure, and ultimately death (10). On the other hand, Giudice A. et al. mention that these clinical conditions in addition to the above-mentioned, can negatively influence the quality of life of patients both at functional and psychosocial level, so it is essential to diagnose the pathology as soon as possible to have management against subsequent complications and achieve together with parents or caregivers an adequate development of the child, thus improving their quality of life (8). In relation to oral manifestations, Yang Il. et al. in their study of patients with PRS exhibited normal overbite and deep bite that could be related to linguoversion of the maxillary and mandibular incisors (12).

Camargo AC. et al. emphasize that the main imaging techniques used for the diagnosis of PRS are: panoramic radiography associated with cephalometry and computed tomography (9). Rodriguez et al. consider that periapical radiographs, bitewing, orthopantomography, and lateral skull teleradiography help to establish a better diagnosis and treatment (5).

Evans K. et al. agree that the first priority of treatment is directed towards the airway, having a surgical success rate of 70% in infants who present isolated PRS, although it is considered that the first line treatment is the prone position allowing the jaw and tongue to fall forward reducing airway obstruction (1). In relation to surgical techniques Gonzalez et al. report that some techniques aggravate the difficulty in swallowing food, causing children to become malnourished, requiring the performance of a gastrostomy by a pediatric surgeon (10).

Morrison et al. consider that there is a lack of high-level evidence regarding the diagnosis, treatment, and long-term prognosis of infants with PRS due to a low incidence of the disease together with the multiple factors involved in the clinical decision and that there are currently no studies of level 1 evidence results (15). However, there are studies such as the one conducted by Rodriguez et al. where he highlights that interdisciplinary treatment is vital given the multisystemic affectation that these patients present. It is considered that specialists should be present during all phases of treatment to benefit the quality of life at the level of the oral cavity of these children (11). Finally, Morrison K. A. et al. indicate that a well-documented care plan based on protocols that include preoperative and postoperative care should be used to know the severity of the disease, so there should be an expectation of a better evolution in care since many questions remain unanswered (15).

4. Conclusion

- Pierre Robin Syndrome is characterized by presenting a clinical triad: micrognathia, glossoptosis, and upper airway obstruction. This pathology, it is frequently associated with the presence of a horseshoe-shaped or U-shaped ogival palate.
- The etiologic mechanism of PRS is currently unclear, although it is worth mentioning that the S0X9 factor is important in the etiopathology of PRS due to its essential role in the regulation of cartilage cells, whose alteration is a primary event for this pathology.
- It is important to identify this pathology before birth by means of different imaging studies mainly: radiographs, computed tomography, and lateral cephalometry in order to evaluate micrognathia, glossoptosis, and tongue posture, and in this way to establish a prenatal diagnosis, the same that allows choosing the first treatments of the neonates.
- Clinical evaluation at birth is vital to recognize the frequent signs of PRS and avoid future complications that may worsen the clinical picture, the earlier the diagnosis is determined the better the prognosis, influencing a better quality of life for patients. In addition, it is essential to distinguish isolated from syndromic PRS to assess the gravity and severity of PRS, with the syndromic form being characterized as the most severe.
- There is agreement in the literature on the treatment of PRS. The best non-surgical treatment to reduce airway obstruction is prone positioning allowing the mandible and tongue to fall forward. However, it should be considered that there are also surgical treatments that are performed when the desired result is not achieved, such

as mandibular osteogenic distraction, being one of the best treatments that provide long-term results. When distraction fails, tracheotomy is an effective intervention.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors agree no conflict of interest.

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