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Enriqueta Pedraza Deutsch
Master of Sciences Student, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Claudio Cabral Romero
Profesor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, CP 64460, Mexico

Gustavo Israel Martinez Gonzalez
Profesor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, CP 64460, Mexico

Hilda Lourdes Muñuzuri Arana
Profesor, Universidad Autónoma de Guerrero, Facultad de Odontología. Acapulco de Juárez de Guerrero, México

Luis Martin Vargas Zuñiga
Profesor, Universidad Autónoma de Guerrero, Facultad de Odontología. Acapulco de Juárez de Guerrero, México

Maria Argelia Akemi Nakagoshi Cepeda
Profesor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, CP 64460, Mexico

Annet Alejandra Mancillas Aguilera
Profesor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, CP 64460, Mexico

Juan Manuel Solis Soto
Profesor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, CP 64460, Mexico

Corresponding Author:
Enriqueta Pedraza Deutsch
Master of Sciences Student, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Pierre robin syndrome, an update from a stomatological point of view

Enriqueta Pedraza Deutsch, Claudio Cabral Romero, Gustavo Israel Martinez Gonzalez, Hilda Lourdes Muñuzuri Arana, Luis Martin Vargas Zuñiga, Maria Argelia Akemi Nakagoshi Cepeda, Annet Alejandra Mancillas Aguilera and Juan Manuel Solis Soto

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Abstract
Introduction: Pierre Robin sequence (PRS) consists of a clinical triad of micrognathia, glossoptosis and airway involvement with variable inclusion of cleft palate. PRS causes obstruction of the upper airway, therefore, it generates respiratory problems and difficulties in ingesting food.
Objective: To analyze specific information on Pierre Robin Syndrome such as etiology, clinical characteristics, diagnosis and treatment with a dental approach.
Methodology: In order to carry out this literature review, an electronic search was necessary using PubMed and Google Scholar with the words Pierre Robin Syndrome and dentistry, treatment, diagnosis and clinical manifestations".
Results: Its etiology still remains uncertain, there are associated genes and environmental theories justifying the reason for this syndrome. The gene most associated with PRS is the SOX9 gene. It consists of a clinical triad of micrognathia, glossoptosis and airway involvement with variable inclusion of cleft palate. Tooth agenesis can occur as an isolated trait or as part of a recognized congenital syndrome such as PRS. Its diagnosis can be by ultrasound, MRI, polysomnography and clinical features. Non-surgical options include prone sleeping position, supplemental oxygen, use of a mouthpiece with velar extension, oropharyngeal or nasopharyngeal tube, non-invasive ventilation and endotracheal tube placement. Surgical options are mandibular osteogenic distraction (MDO) and tongue lip ligation.
Conclusion: PRS requires a comprehensive approach from the medical staff, maxillofacial surgeon and dentist. The main dental characteristics are agenesis, hypodontia and taurodontism.

Keywords: Pierre robin syndrome, obstructive sleep apnea, diagnosis, treatment, oral manifestations

1. Introduction
Pierre Robin sequence (PRS) consists of a clinical triad of micrognathia, glossoptosis and airway involvement with variable inclusion of cleft palate [1, 2]. Because of its characteristics, PRS usually causes obstruction of the upper airway, thus leading to respiratory problems and difficulty in swallowing food [3, 4]. It is a well-known phenomenon, but it is still associated with considerable morbidity and even mortality if not well treated [5]. The incidence of cases is 1:8000 to 1:14000 births [6]. Typical symptoms are hypoxemia, noisy breathing, snoring, stridor, cyanosis, bradycardia, feeding difficulties and growth retardation [7].
PRS has 3 classifications: Syndromic PRS which is associated with known syndromes such as Stickler, Treacher Collins and Velocardiofacile syndromes. PRS associated with other anomalies, but with a specific syndrome. It is considered non-syndromic PRS when the sequence has no other anomalies or syndrome [8]. Although it is a rare coincidence, Pierre Robin syndrome can still occur in identical twin infants [9]. The study of this syndrome is of importance, as there are not enough publications about the dental management of Pierre Robin syndrome. It is important to emphasize a dental approach because this anomaly involves the craniofacial complex. Having knowledge of this syndrome gives us a broader view of its clinical and dental approach. The objective of this study is to analyze information regarding Pierre Robin syndrome, such as etiology, clinical characteristics, diagnosis and conservative

and surgical treatment, with a dental approach to improve the prognosis for life and health, decreasing the risk of morbidity.

2. Materials and Methods

Articles on the subject published through the PubMed, SCOPUS and Google Scholar databases were analyzed, with emphasis on the last 5 years. The quality of the articles was evaluated using guidelines, i.e., identification, review, choice and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews. The search was performed using Boolean logical operators AND, OR and NOT. The search was performed using Boolean logical operators AND, OR and NOT; with the keywords: "Pierre Robin Syndrome", "Obstructive Sleep Apnea", "diagnosis", "treatment", "oral manifestations". The keywords were used individually, as well as each of them related to each other.

3. Results & Discussion

3.1 Etiology

The etiology of the PRS still remains uncertain, however, there are associated genes and environmental theories justifying the reason for this syndrome [8]. Different mutations have been observed in patients with PRS such as deletion, translocation, duplication, single nucleotide polymorphism, nonsense mutation, breakpoint mutation, splice defect mutation, insertion and inversion [10].

The gene mostly associated with syndromic and non-syndromic PRS is the SOX9 gene [11]. The reciprocal translocation t (4; 6) (q22; p21) was identified in a family with PRS. Whole genome sequencing detected breakpoints in the intragenic regions of BMRP1B and GRM4 [12]. In an isolated case of a girl with PRS, a 14.34 Mb terminal deletion of chromosome 10q was found [13].

The mechanistic theory holds that early in the first trimester, if mandibular growth is abnormal, the tongue cannot follow the normal growth trajectory causing glossoptosis [8,14]. The neurological maturation theory speaks of a delay in the neuromuscular development of the tongue. The theory of mandibular compression proposes that external forces cause the fetal head to flex, compressing the mandible against the chest [15].

The etiology is not yet known, only that the most associated gene is SOX9 and it is believed that there may be prenatal factors that trigger it.

3.2 Diagnosis

Ultrasonography is currently the most widely described prenatal screening modality for detecting PRS. Examination of the fetal face is performed using a two-dimensional ultrasound probe in multiple planes [16]. Antenatal magnetic resonance imaging (MRI) can also be used to determine the shape and position of the tongue to predict postnatal PRS [17, 18].

To determine the severity of airway obstruction in patients with PRS, a physical examination is performed to measure the degree of micrognathia. Computed tomography, cephalometric imaging, or polysomnography (PSG) for determining the degree and type of airway compromise. And laryngoscopy/bronchoscopy to rule out other major airway diseases [19,20]. Genetic analysis in PRS allows differentiation of syndromic PRS from isolated PRS [21]. Ultrasonography and MRI can be used for prenatal diagnosis. If PRS is not detected prenatally at birth, its clinical features can be observed and a TC scan, oximetry or polysomnography can be performed, and these tests will yield an accurate diagnosis.

3.3 Oral Clinical Features

Robin sequence is characterized by mandibular retrognathia, airway obstruction and glossoptosis; 80%-90% also have cleft palate [22]. Because of its clinical features of glossoptosis and retrognathia, there is mechanical obstruction of the upper airway, so PRS is an important cause of neonatal obstructive sleep apnea (OSA) [23].

Glossoptosis in PRS refers to posterior displacement of the tongue from the oral cavity [17]. Glossoptosis was classified as severe when the tongue was in an upright and posterior position, moderate in case of posterior ptosis but no upright tongue position and mild in case of elevation of the sublingual ridges [24].

Retrognathia is a term used to describe an unusual position of the mandible. Retro implies that there is poor growth and 'gnathia' means over the jaws (particularly the mandible) [25]. Retrognathia in patients with PRS was classified as "severe" when the lower lip was completely covered by the upper lip; moderate when it was partially apparent; and mild when it was completely [24]. Predominant skeletodental patterns included Class II relationship, posteriorly positioned maxilla and mandible, hyperdivergent pattern, high gonial angle, small mandibular body length to anterior skull to base ratio, linguoversion of upper incisors, and linguoversion of mandibular incisors [26]. The main dental organ disorders related to PRS are agenesis, microdontia, dwarf roots, taurodontism and supernumerary teeth [8, 12]. Tooth agenesis can occur as an isolated feature or as part of a recognized congenital syndrome, such as PRS [27]. Bilateral agenesis of the lower second premolars is a frequently observed pattern among patients with PRS. Patients with PRS and cleft palate are more likely to have hypodontia than those with isolated cleft palate or unilateral cleft lip [28]. Cases have also been shown of patients with PRS who have eruption cysts making airway opening even more difficult [29].

The characteristic triad in PRS is glossoptosis, retrognathia and airway obstruction, highly related to cleft palate. The main dental anomalies are agenesis, microdontia, taurodontic dwarf roots and supernumeraries.

3.4 Conservative and Surgical Treatment

PRS can present as a perinatal emergency when the tongue in retroposition obstructs the airway and the ability to feed [15,30]. The first option in these cases is to perform an emergency tracheostomy so that the patient can adequately saturate and eliminate the cyanotic state [31]. Non-surgical options in non-emergency cases include prone sleeping position, supplemental oxygen, use of a mouthpiece with velar extension, oropharyngeal or nasopharyngeal tube, non-invasive ventilation and placement of an endotracheal tube [32].

Within the conservative treatment, the pre-epiglottic rod plate (PEBP) is used [33]. It is an orthodontic device that increases oxygen levels in the blood, a decrease in respiratory frequency and a normalization of skin color [34, 35]. It eliminates functional disturbances of mandibular growth, reduces and, in some cases, eliminates the need for surgical intervention [36]. High-flow nasal oxygenation and/or continuous positive airway pressure is given first-line respiratory support, followed by PEBP for 3-5 months [37]. However, mandibular micrognathia in patients with the Pierre Robin sequence managed conservatively may not resolve over time and may require surgical intervention [38]. Surgical

treatments are based on mandibular distraction osteogenesis (MDO) and tongue-lip adhesion [39]. Tongue-lip adhesion has been demonstrated to improve OSA [40]. Both treatments are effective alternatives to tracheostomy for patients who fail conservative treatment and improve feeding [41]. MDO is a technique that improves tongue-based airway obstruction and avoids tracheostomy in patients with severe expressions of Pierre Robin sequence [42]. The goal of mandibular distraction in RPS is to maximally expand the oropharyngeal airway [43]. It is unclear whether MDO will replace the possible need for future orthognathic surgery [44].

Conservative treatment in patients with PRS includes nasal oxygenation, velar extension device, pre-epiglottic plate, prone position and endotracheal tube. Surgical treatment includes tracheostomy, osteogenic distraction and lip tongue tie.

4. Conclusiones

PRS consists of a clinical triad of micrognathia, glossoptosis and airway involvement with variable inclusion of cleft palate. Its etiology still remains uncertain, there are associated genes such as SOX9 and environmental theories justifying the reason for this syndrome. Diagnosis can be by ultrasound, MRI, polysomnography and clinical features. Non-surgical options include prone sleeping position, supplemental oxygen, use of a mouthpiece with velar extension, oropharyngeal or nasopharyngeal tube, non-invasive ventilation and endotracheal tube placement. Surgical options are mandibular osteogenic distraction and tongue-lip adhesion.

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