BJDOR
BRAZILIAN JOURNAL OF DENTISTRY AND ORAL RADIOLOGY

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PUBLICAÇÕES CIENTÍFICAS DE ACESSO ABERTO

Review

Multidisciplinary treatment of Pierre Robin sequence: a review

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Abstract: The Pierre Robin Sequence (PRS) is defined as a triad of anomalies characterized by micrognathia and / or retrognathia, glossoptosis and upper airway obstruction. Most patients have cleft palate. Airway obstruction and feeding difficulties are the most common manifestations and more severe in the neonatal period in the SPR. The priority in treatment should be to maintain airway patency. In this study we observed a journal of literature and the surgical and non-surgical treatment and multidisciplinary Hospital Infantil Albert Sabin with maxillofacial surgeons, orthodontists, neonatologists, pediatricians, pediatrics surgeons, plastic surgeons, and speech therapists for patients with SPR.

Keywords: Pierre Robin Syndrome; Cleft palate; Genetic syndromes.

Citation: Carneiro DTO, Cunha Filho JF, Silva RN. Multidisciplinary treatment of Pierre Robin sequence: a review. Brazilian Journal of Dentistry and Oral Radiology. 2022 Jan-Dec;1:bjd10.

doi: https://doi.org/10.52600/2965-8837.bjdor.2022.1.bjd10

Received: 3 April 2022
Accepted: 12 May 2022
Published: 17 July 2022

1. Introduction

Historically, Fairbairn in 1846, and Lannelongue and Menard in 1891, were the first to describe Pierre Robin Syndrome in patients who exhibited micrognathia, cleft palate, and glossoptosis. Pierre Robin, a French stomatologist, in 1923, pointed to the association of glossoptosis and micrognathia and later added references to cleft palates in his early writings eleven years afterwards [1-3]. In 1974, the triad was named Pierre Robin Sequence (PRS) [4]. The term "syndrome" is used when there is a simultaneous presence of several abnormalities originating from a single etiology. The term "sequence" is used when several abnormalities arise from a cascade of events initiated by a single malformation [2, 4]. Thus, the term Pierre Robin Syndrome came to be known as Pierre Robin Sequence. Therefore, the well-known PRS has been designated as a non-specific symptomatic complex that can occur in various isolated situations, associated with some syndrome, or associated with other developmental errors, which together do not correspond to a specific syndrome [2].

PRS is a triad of anomalies characterized by micrognathia and/or retrognathia, glossoptosis, and obstruction of the upper airways [5]. A cleft palate is present in 90% of the cases [3, 6], which makes this clinical evidence not essential for diagnosis, as not all affected by PRS present this finding [7]. Airway obstruction and feeding difficulties are the most common and severe manifestations in the neonatal period. There is heterogeneity of clinical manifestations [8], observing mild expressions of respiratory and feeding difficulties to severe asphyxia crises, which can lead to death if there is no rapid medical intervention [9, 10]. Syndromic craniofacial changes may accompany PRS, such as Stickler syndrome, Treacher Collins syndrome, and Neger syndrome, for example [6].

The treatment of PRS can occur through non-surgical therapy or surgical intervention. Some newborns can be placed in the considered ideal posture, prone, until there is adequate growth of the jaw. This induces the jaw and tongue to take a more inferior and

anterior position, freeing the upper airways. However, the failure of non-surgical therapies may lead the patient to surgical intervention through glossopexy, tracheostomy, or mandibular distraction osteogenesis [10]. In the Outpatient Clinic of the Integrated Care Center for Cleft Individuals (NAIF) at the Albert Sabin Children's Hospital in Ceará (HIAS-CE), patients with craniofacial alterations receive diagnosis after a multidisciplinary clinical evaluation and are treated according to the degree of respiratory and nutritional impairment, which can be non-surgical/conservative or surgical.

The aim of this article is to clarify the etiopathogenesis, clinical manifestations, diagnosis, and treatment of PRS and to highlight a care protocol for these patients.

2. Methodology

A review was conducted in the literature using major digital bibliographic cataloging sources (Pubmed, Scopus, and Lilacs) utilizing descriptors (DeCS) such as Pierre Robin Syndrome, cleft palate, cleft lip, genetic syndromes, in both English and Portuguese languages. The inclusion criteria adopted were publications classified as original articles, studies on humans, clinical case reports, and publications that discussed Pierre Robin Sequence. Conference abstracts were excluded. Based on the literature and the treatment experience for these patients at the Albert Sabin Children's Hospital, a multidisciplinary treatment protocol was described.

3. Results

3.1 Etiopathogenesis

The estimated prevalence of Pierre Robin Sequence (PRS) is 1:8,500 live births, with 80% associated with some syndrome. The sex distribution ratio is 1:1, except in the X-linked form, which includes cardiac malformations and abnormal positioning of the feet [4]. The etiology of PRS has been discussed over time by many authors [13, 2, 10]. Some have proposed theories involving abnormal intrauterine fetal positions during development, leading to micrognathia and repositioned tongue, which results in obstruction of palatal cleavage [13]. There are beliefs in the role of genetic factors, supported by reports of family histories [2, 10]. Others, while not accepting the above theory, do not consider heredity as a decisive factor in the development of the disease [2, 10].

However, a 2007 cytogenetic study by Jakobsen et al. on individuals with isolated PRS suggested that clinical manifestations could be caused by genetic mutations in the SOX9 and KCNJ2 genes [14]. There are also theories that PRS may involve a delay in neurological maturation, evidenced by delayed conduction in the hypoglossal nerve resulting in motor deficits of the tongue and pharyngeal pillars [12]. Various syndromes accompany the classic triad of PRS. The most common is Stickler syndrome or hereditary arthro-ophthalmopathy, where PRS is a result of intrinsic mandibular hypoplasia due to a deficit in connective tissue penetration through the palate. This is followed by Velocardiofacial syndrome (deletion of chromosome 22q11.2), Treacher Collins, Nager, and fetal alcohol syndrome [15].

3.2 Clinical manifestations

Pierre Robin Sequence (PRS) is characterized by micrognathia, glossoptosis, and obstruction of the upper airways with or without cleft palate in newborns [16]. Arancibia et al., in 2006, reported that micrognathia is present in 91% of cases, glossoptosis in 70% - 85%, ocular anomalies in 10% - 30% with a low frequency of nasal anomalies [4]. Barrientos et al., in 2010, also stated that the frequency of macroglossia and ankyloglossia is 10% - 15%, cleft palate ranges from 14% - 91%, and ear anomalies are found in 75% of cases [12]. Patients present with varying degrees of upper airway obstruction. In more severe cases, episodes of asphyxiation, apnea, cyanosis [15], and feeding difficulties are evident. The situation is even more critical in the neonatal period [2].

Respiratory obstruction in PRS is not always caused by glossoptosis; other mechanisms may be involved. Ribeiro et al., in 1999, demonstrated that in 1992, a flexible fiber

optic nasopharyngoscope was used in newborns to investigate upper pharyngeal obstruction in patients with PRS. Four different types of upper airway obstruction mechanisms were identified. Type 1: posterior movement of the tongue's dorsum to the posterior pharyngeal wall. Type 2: in addition to the anterior movement, the tongue compresses the soft palate or remnants of the cleft palate against the posterior pharyngeal wall, resulting in a juxtaposition of the tongue, velum, and posterior pharyngeal wall in the upper position of the oropharynx. Type 3: the lateral pharyngeal walls move medially, opposing each other. Type 4: the pharynx contracts in a circular or sphincteric manner in all directions [16].

Micrognathia is characterized by a retraction of the lower dental arch by 10mm to 12mm relative to the upper arch. The jaw has a small body, an obtuse genial angle, and a posteriorly located condyle. Jaw growth occurs during the first year, with the profile tending to normalize between 5 and 6 years [12, 2]. Newborns with PRS may have impairments in various systems. The cardiovascular system, in some cases, is affected with pulmonary stenosis, persistent foramen ovale, atrial septal defect, and primary pulmonary hypertension. In the musculoskeletal system, syndactyly, dysplastic phalanges, polydactyly, clinodactyly, joint hypermobility, and oligodactyly in the upper limbs may occur.

In the central nervous system, delayed language development, epilepsy, psychomotor developmental delay, and hydrocephalus are reported. Genitourinary defects such as cryptorchidism and hydrocele are also mentioned in the literature. Lower limb malformations involving the femur, knees, and tibia are observed [4]. Obstructive Sleep Apnea Syndrome (OSAS) may be triggered in infants with PRS due to the complex condition of the craniofacial skeleton that protects the upper airways. OSAS in children has a multifactorial etiology and occurs due to structural obstructive factors (craniofacial changes, micrognathia, tonsillar hypertrophy, and laryngomalacia) and neuromotor factors (pharyngeal muscle hypotonia and neurological syndromes) [17, 18].

3.3 Diagnostic

The morphological ultrasonographic examination is of fundamental importance for the prenatal diagnosis of Pierre Robin Sequence (PRS), with signs potentially visible as early as the 13th week of gestation. However, the identification of cleft lip and palate is only possible between the 28th and 30th weeks of gestation [19]. Thus, these clefts, being the most prevalent craniofacial malformations, can be recognized through this examination, which implies appropriate prenatal counseling for pregnant women [20, 4]. Micrognathia is another anomaly that can be visualized during the examination. Although this condition is present in various anomalies and the fetal prognosis of micrognathia is poor, it can already indicate some developmental alteration, as evidenced by Morokuma et al. in 2010 [21]. In the newborn, the characteristic manifestations of Pierre Robin Sequence are quite evident due to the presence of the characteristic triad (micrognathia, glossoptosis, upper airway obstruction with or without cleft palate). Therefore, given the present signs, the diagnosis is clinical.

3.4 Treatment

The treatment of patients with isolated Pierre Robin Sequence (PRS) or associated with a syndrome is carried out in a multidisciplinary manner involving a maxillofacial surgeon, plastic surgeon, neonatologist, pediatrician, and speech therapist. The goal is to assess the maxillo-mandibular relationship, the maintenance of oronasopharyngeal anatomy, the location of upper airway obstruction, and feeding difficulties. A multidisciplinary team is ideal for diagnosing and developing an appropriate treatment plan [15].

Although some institutions [10] have developed their own treatment protocols, there is still no absolute consensus on the treatment for individuals with Pierre Robin Sequence [9]. The different types of respiratory obstruction found were classified into types 1, 2, 3, and 4, and the nasopharyngoscopic findings guide the type of treatment and prognosis [10, 2]. Treatment is basically approached from two fronts; non-surgical conservative and surgical, with the latter being carried out based on the basic criterion of the failure of conservative therapy.

3.5 Non-surgical management

The most common conservative treatments include postural treatment, also known as the prone position with the child in a ventral decubitus; nasopharyngeal intubation, which involves inserting an intubation cannula with a diameter of 3 to 3.5mm, introduced from 7 to 8cm through the nostril to the pharynx and cut 1cm outside the nostril [10]. More recently, the use of palatal obturator plates with a device in the anterior region of the plate to direct the correct positioning of the tongue has been employed.

The prone position is indicated when the child presents with mild respiratory and feeding difficulties. Improvement is not only attributed to the prone position but primarily to cervical extension. Nasopharyngeal intubation is indicated when respiratory patterns are significantly altered, leading to a more severe condition such as episodes of cyanosis, apnea, pallor, significant respiratory effort, and a drop in oxygen saturation to values of 90% or less. The goals of nasopharyngeal intubation are to maintain a good respiratory pattern, reduce respiratory effort, keep saturation above 90%, improve oral food acceptance, consequently reducing the time of gastric tube use, and promote weight gain [10]. Conservative therapy is carried out in the first 15 days after diagnosis with monitoring of the patient's clinical progression, as longer periods may induce problems associated with the use of tubes and increased hospitalization time. Surgical procedures such as glossopexy, tracheostomy, and the installation of bilateral mandibular distractors are indicated when conservative therapy is not successful [10].

3.6 Surgical management

Type 1, obstruction originating from true lingual ptosis, is the most commonly found respiratory obstruction in Pierre Robin Sequence, accounting for approximately 80% of cases and allowing a better prognosis. Glossopexy, to relieve respiratory discomfort, is only indicated in type 1 obstruction cases that do not improve with nasopharyngeal intubation over a maximum period of 15 days [10]. Glossopexy was initially described by Douglas in 1946 [15] and has since undergone adaptations for better surgical practice. The procedure involves fixing the tongue to the lower lip and jaw; however, it is not always possible to maintain the tongue's position for long periods, so it should be applied with proper indication [2].

In 1992, Argamaso performed glossopexy using his own modified technique on 24 infants with PRS and a surgical indication for the procedure. In all cases, rapid relief of the upper airways was observed [22]. Patients affected by type 2, 3, and 4 obstructions are typically associated with genetic syndromes, neurological problems, and other malformations [2]. Marques et al., in 2005, observed that patients with type 2 obstruction required tracheostomy in 50% of cases to relieve respiratory discomforts. In cases 3 and 4, tracheostomy was the only treatment that provided relief in respiratory obstruction [10]. Another surgical procedure is mandibular distraction osteogenesis. It is a recent technique being used to treat the respiratory complication of PRS [2]. It consists of mandibular elongation from a bone callus allowing the correct accommodation of the tongue in the oral floor with a distractor anchored bilaterally at the angle of the jaw [6].

4. Discussion

The care of patients with Pierre Robin Sequence (PRS) in non-specialized services can be an unpleasant experience due to the great complexity of the case. Immediate pediatric management is necessary through non-surgical and/or surgical therapy in the short and medium term, especially regarding the maintenance of upper airways and feeding difficulties [16]. Clinical management and care protocols are not always known by professionals, which can lead to the newborn's death. Respiratory obstruction of the upper airways is common in children with labiopalatine fissures. These fissures may be present in patients with PRS, whether associated with genetic syndromes or isolated. Some authors [12,4] state that there is a variation in the percentage of infants with PRS associated with palatal clefts, ranging from 14% to 91% of cases, and other authors [15,23] with 80%

of cases. In infants treated at the NAIF of HIAS, it was observed that all patients had palatal clefts.

Clinically, the triad is expressed by obstruction of the upper airways and feeding difficulties (uncoordinated sucking/swallowing with breathing) which become more frequent and severe in the neonatal period [12,23]. Diagnosis at the NAIF outpatient clinic is carried out after the child's arrival at the hospital by a multidisciplinary team consisting of neonatologists, pediatricians, plastic surgeons, maxillofacial surgeons, orthodontists, and speech therapists. The severity of the neonate's respiratory and feeding impairment is then assessed. The decision for conservative or surgical procedures is made jointly by the team.

Guidance to parents for the correct posture of the child (prone position) is given as soon as PRS is diagnosed with mild impairment of breathing and nutrition. Depending on the severity of the clinical situation, the placement of a nasopharyngeal tube is performed to restore respiratory patterns. These conservative procedures are firstly adopted. The same speech therapy technique that facilitates oral feeding of infants with PRS, used at the Hospital for Rehabilitation of Craniofacial Anomalies at the University of São Paulo (HRAC/USP) [10], is adopted by HIAS-CE. This technique is called facilitative speech therapy feeding technique (TFFA) and is performed by speech therapists.

The TFFA involves non-nutritive sucking stimulation using pacifiers, massages to relax and anteriorize the tongue, manual support to sustain the jaw, a soft long nipple bottle with a hole enlarged to one millimeter, placement of the nipple over the tongue, symmetrical global posture, and rhythmic movements of the nipple in the oral cavity during nutritive sucking [10]. Gradually, the neonate's food transition from the tube (usually nasogastric or orogastric) to oral feeding is carried out, a process that is gradual and successive until the baby can feed exclusively orally with total safety, thus ensuring adequate development and weight gain.

With the failure of non-surgical procedures, surgical interventions are planned and executed. Glossopexy is one of the surgical procedures performed on patients with PRS treated at HIAS. After the surgical procedure, the young patient is released to resume speech therapy practices (TFFA) to further improve breathing and nutrition patterns. After 15 days post-surgery, the release of the tongue to the lip and the respiratory patterns of the neonate are re-evaluated. The elimination of respiratory discomfort with glossopexy treatment will minimize or even eliminate feeding difficulties since it will clear the upper airways, thus contributing to the proper nutritional development of the patient, which will certainly ensure that the PRS carrier is adequately prepared for palatoplasty when there is a presence of a cleft palate, after 12 months of birth. There is not yet a consensus on the risks and benefits of mandibular distraction osteogenesis for patients with PRS. Therefore, mandibular distraction osteogenesis is not part of the surgical protocol carried out in this group of patients at HIAS-CE.

5. Conclusion

Pierre Robin Sequence has heterogeneity in its clinical characteristics which allows diagnosis in four different clinical patterns, depending on respiratory involvement. Multidisciplinary and interdisciplinary attention is necessary for treatment, as many components of the stomatognathic system are involved. Conservative treatment is the first choice for these patients at HIAS. However, its failure leads to the performance of glossopexy or tracheostomy. Speech therapy follow-up is carried out immediately after the surgical procedure to reorganize the motricity of sucking for correct oral feeding.

Funding: None.

Research Ethics Committee Approval: We affirm that the participant consented to the research by endorsing a clear consent document, and the investigation adhered to the ethical standards outlined in the Helsinki Declaration.

Acknowledgments: None.

Conflicts of Interest: None.

Supplementary Materials: None.

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