DOI: https//doi.org/10.13037/ras.vol18n66.7148

Review Article

Recebido em: 17/07/2020 | Aceito em: 16/12/2020

Multidisciplinary aspects and secondary clinical manifestations of Pierre Robin sequence: an integrative review

Aspectos multidisciplinares e manifestações clínicas secundárias da sequência de Pierre Robin: uma revisão integrativa

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Abstract

Introduction: Pierre Robin Sequence (PRS) is characterized by micrognathia, glossoptosis and cleft palate. Clinically, the consequences of this alteration include respiratory impairment and feeding difficulties. However, secondary clinical signs related to this condition, as well as the relevance of multidisciplinary care and the training of caregivers are rarely discussed in the literature. **Objective:** This study aimed to perform an integrative review about secondary clinical manifestations and multidisciplinary aspects related to the Pierre Robin Sequence PRS. **Material and Methods**: For this purpose, a bibliographic research on this topic was carried out in scientific literature databases *Pubmed*, *Scielo*, *BVS-Lilacs* and *BBO*, including from literature reviews, case reports, prospective and retrospective studies, randomized clinical studies to systematic reviews and meta-analyzes, published between January 2014 and December 2019 in English or Portuguese. Molecular investigations and animal studies, absence of the term "*Pierre Robin*" in the title and/or abstract, as well as, impossibility of accessing the full text version, or articles with main theme diverging from the proposed research question (*"What are the secondary clinical manifestations and multidisciplinary aspects related to Pierre Robin Sequence?"*) were excluded from the analysis. The findings of the studies selected in terms of pre-established criteria were discussed in a descriptive way. **Results:** Initially, bibliographic research showed 108 articles, which 28 answered the purpose of this review. Multidisciplinary aspects related to the PRS included: diagnosis, etiopathogenesis of the disease, patient mortality rate, cleft dimensional evaluation and importance of promoting self-care. The

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secondary clinical manifestations of the disease consisted of dental anomalies and bone, muscle and cardiac alterations. **Conclusion:** The multidisciplinary aspects related to PRS showed the complexity of the diagnosis and etiopathogenesis of this disorder the higher risk of mortality and more extensive cleft palates in affected individuals, as well as the need to promote self-care to parents of babies with PRS in order to reduce the risks of complications and improve quality of life of these patients. Whilst dental and/or bone, muscle and cardiac malformations, characterized as secondary clinical manifestations of PRS, may feature an isolated factor or a syndromic condition.
Keywords: Cleft lip, cleft palate, Pierre Robin Syndrome.
Resumo

Introdução: A Sequência de Pierre Robin (SPR) é caracterizada por micrognatia, glossoptose, e presença de fissura palatina, acarretando, como consequências desta alteração, comprometimento respiratório e dificuldade em se alimentar. No entanto, os sinais clínicos secundários relacionados a esta doença, bem como, a relevância do atendimento multidisciplinar e da capacitação dos cuidadores raramente são discutidos na literatura. **Objetivo:** Realizar uma revisão integrativa acerca das manifestações clínicas secundárias e dos aspectos multidisciplinares relacionados à SPR. **Materiais e Métodos:** Para tanto, um levantamento bibliográfico sobre o tema foi realizado nas bases de dados de literatura científica *Pubmed*, *Scielo, BVS-Lilacs* e *BBO*, incluindo desde de revisões de literatura, relatos de casos, estudos prospectivos e retrospectivos, estudos clínicos randomizados a revisões sistemáticas e meta-análises, publicadas entre janeiro de 2014 e dezembro de 2019 em língua inglesa ou portuguesa. Investigações moleculares ou estudos em animais, ausência do termo "*Pierre Robin*" no título e/ou resumo, bem como, artigos não acessíveis na íntegra, ou trabalhos cujo tema principal divergia da questão norteadora proposta (*"Quais são as manifestações clínicas secundárias e os aspectos multidisciplinares relacionados à Sequência de Pierre Robin?"*), foram excluídos da análise. Os achados dos estudos selecionados pelos critérios pré-estabelecidos foram discutidos de maneira descritiva. **Resultados:** Inicialmente 108 artigos foram encontrados no levantamento bibliográfico, e destes, 28 artigos responderam o propósito desta revisão. Os aspectos multidisciplinares relacionados à SPR incluíram os seguintes tópicos: diagnóstico, etiopatogenia da doença, taxa de mortalidade dos pacientes, avaliação dimensional da fissura e importância da promoção do autocuidado. As manifestações clínicas secundárias da doença compreenderam anomalias dentárias e alterações ósseas, musculares e cardíacas. **Conclusão:** Os aspectos multidisciplinares relacionados à SPR mostraram a complexidade do diagnóstico e etiopatogenia dessa alteração, o maior risco de mortalidade e fissuras palatinas mais extensas em indivíduos acometidos, bem como, a necessidade da promoção de autocuidado aos familiares de bebês com SPR para redução dos riscos de complicações e aumento qualidade de vida desses pacientes. Enquanto que, as malformações dentárias e/ou ósseas, musculares e cardíacas, caracterizadas como manifestações clínicas secundárias da SPR, podem se apresentar como um fator isolado ou compor uma condição sindrômica.
Palavras-chave: Fenda labial, fissura palatina, Síndrome de Pierre Robin.

Introduction

Pierre Robin Sequence (PRS) is a condition composed of retro- or micrognathia, glossoptosis, and usually, the presence of cleft palate[1-10]. Cleft palate in patients with PRS are traditionally described as "U" or "V" shape, predominating the occurrence of wider U-shaped cleft palate[1,4-7]. Popularly, the aspect of Pierre Robin's triad is called "Bird face appearance"[11,12]. The prevalence of PRS varies between 1:8000[8,12-14] and 1:30000[9] live births.

The term "Pierre Robin Sequence" is assigned, as it is believed that micrognathia is a precursor of glossoptosis and cleft, since a primary defect occurs in the Meckel's cartilage, precursor of the mandible. Mandibular hypoplasia subsequently causes labial enlargement, abnormal tongue position, and

consequently, damage to the cleft palate closure[1,4,6,8,15,16]. PRS can occur isolated or in association with other anomalies and syndromes[1-9,12,13,16-26], being Stickler Syndrome the most common[1-9,12,13,19,21,23,25]. While "Pierre Robin Syndrome" refers to the association of the Pierre Robin Sequence with a known syndrome[1]. The mortality rate is higher in this condition, due to severe respiratory impairment and the risk of malnutrition[8,17].

The malformation of PRS causes different degrees of respiratory obstructions and feeding problems, which require care from a multidisciplinary team and qualified caregivers, especially in the neonatal period[3,5,8,14,27,28]. Treatment varies according to the severity of the airway impairment and feeding capacity, including from conservative techniques to surgical procedures[8]. There is a consensus that these problems require early diagnosis for the immediate performance of adequate treatment, preventing complications that can lead to death[8,13,17,19].

Although respiratory impairment and feeding difficulties, consequences of the clinical aspect of PRS, as well as the respective treatment alternatives, are quite consolidated[2,3,5,8], secondary clinical signs related to this disease are rarely investigated and discussed. As well, the relevance of multidisciplinary care and training of caregivers is also poorly evidenced in the literature.

Integrative reviews have the potential to promote review studies in several areas of knowledge, maintaining the methodological rigor of systematic reviews, which establish systematic criteria for selecting articles, collecting and analyzing data, and consequently produce information with scientific evidence[29,30]. Thus, seeking to present the particularities of unusual clinical manifestations and emphasize the importance of multidisciplinary care for these patients, this integrative review may bring important contributions to integral reception and guidance for comprehensive treatment in all necessary aspects.

Therefore, the aim of this study was perform an integrative review about secondary clinical manifestations and multidisciplinary aspects related to the Pierre Robin Sequence.

Materials and methods

The integrative literature review was performed through a computerized search in the databases *Pubmed* (*http://pubmed.ncbi.nlm.nih.gov*), *Scielo* (*http://scielo.org*), *BVS-Lilacs* (*http://bvsalud.org*) and *BBO* (*http://bases.bireme.br*), using as a search strategy the combination of descriptors (MeSH/BVS-DECS): *"Cleft Lip"* AND/OR *"Cleft Palate"* AND *"Pierre Robin Syndrome"*. The guiding question of this review was: *"What are the secondary clinical manifestations and the multidisciplinary aspects related to the Pierre Robin Sequence?"*.

To perform this review, methodological criteria were pre-established, following Evidence-Based Practice[29,30]. The selection of articles considered the inclusion, from literature reviews, case reports, prospective and retrospective studies, randomized clinical studies (RCTs) to systematic reviews and meta-analyses, published in English or Portuguese, between January 2014 and December 2019, and available in full. The exclusion criteria were: molecular investigations; animal studies; Absence of the term "Pierre Robin" in the title and/or abstract; as well as articles not accessible in full; or studies whose main theme diverged from the guiding question of this review, such as: "respiratory impairment", "feeding difficulties" and "treatment alternatives" related to PRS.

The survey of the articles was carried out in February 2020, independently, by two previously trained authors, who selected an initial list of

references. To determine the sample of articles to be analyzed in full, the initial selection of references was reviewed jointly by the two researchers, applying the inclusion and exclusion criteria described, and in case of disagreements, a third evaluator established the consensus.

The selected studies were analyzed in full, and studies that answered the guiding question of this review, investigating "secondary clinical manifestations" and the "multidisciplinary aspects" related to PRS, were tabulated in a predetermined instrument, addressing: name of the author (year); type of study; the country in which it was developed; publication language; title; purpose; and the main theme of the investigation. The final sample of articles was discussed descriptively.

Results

Through search strategies and application of inclusion filters, 108 articles were found, obtained predominantly in the *Pubmed* database (90.7%), followed by the *BVS-Lilacs* and *BBO* (5.6%) and *Scielo* (3, 7%). After reading the title and abstract, 70 articles were selected and analyzed in full, and of these, 28 composed the final review analysis (Figure 1). The Multidisciplinary aspects related to the PRS included the following topics: diagnosis; etiopathogenesis of the disease; patient mortality rate; cleft dimensional evaluation; and importance of promoting self-care. The secondary clinical manifestations of the disease consisted of dental anomalies and bone, muscle and cardiac alterations (Table 1). The bibliographic data, the purpose and the topics covered by each study included in this review are described, and organized in chronological order of publication, in Table 2.

Figure 1 - Flowchart of the selection of articles included in the integrative review.

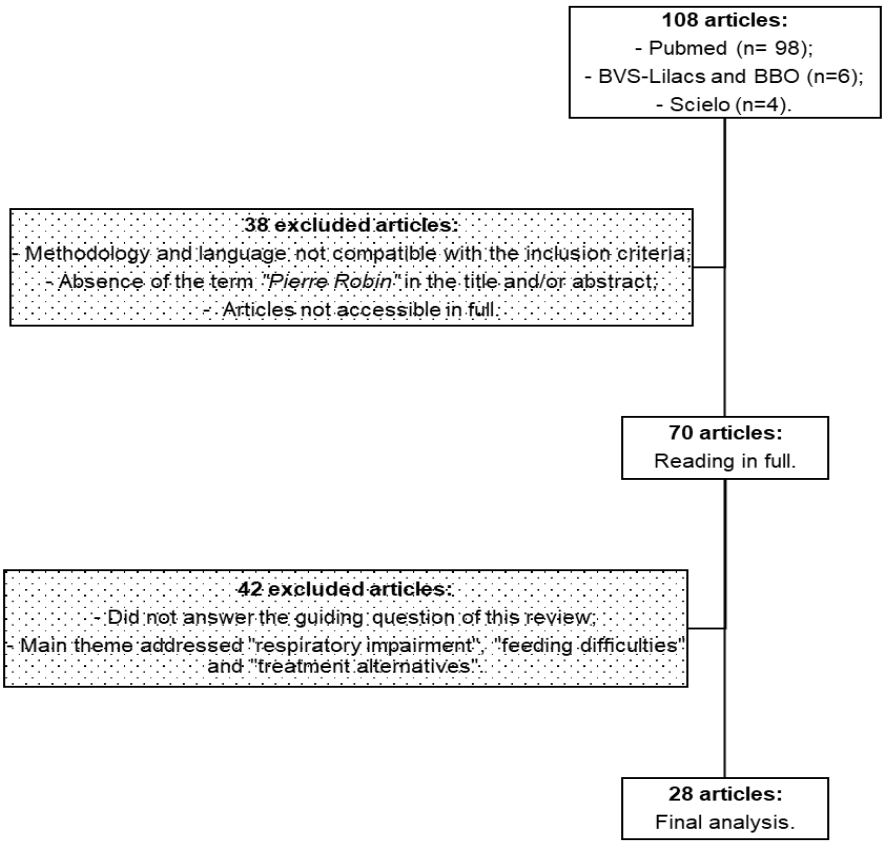

Table 1 - List of topics covered in the articles included in the final analysis.

MAIN THEME	TOPICS	AUTHORS
MULTIDISCIPLINARY ASPECTS	- DIAGNOSIS - ETIOLOGY - PATHOGENY - MORTALITY	van Nunen et al. (2014)[17]; Basart et al. (2015)[2]; Filip et al. (2015)[3]; Lind et al. (2015)[4]; Oliveira et al. (2015)[13]; Breugem et al. (2016)[5]; Resnick et al. (2018)[6]; Hsieh et al. (2019)[8]; Cleary et al. (2020)[10].
	- DIMENSIONAL ASSESSMENT OF THE CLEFT PALATE	Godbout et al. (2014)[1]; Lambert et al. (2016)[15]; Do et al. (2019)[7].
	- PROMOTION OF SELF-CARE	Trettene et al. (2016)[27]; Demoro et al. (2018)[28]; Souza et al. (2018)[14].
SECONDARY CLINICAL MANIFESTATIONS	- DENTAL ANOMALIES	Andersson et al. (2015)[18]; Smalen et al. (2017)[22]; Mateo-Castillo et al. (2019)[9]; Rojare et al. (2019)[26].
	- BONE AND MUSCLE ALTERATIONS	Rosa et al. (2015)[19]; Faraz et al. (2016)[11]; Lopes et al. (2016)[20]; Waldrop et al. (2017)[23]; Pinto et al. (2018)[25]; Robbins et al. (2019)[16].
	- CARDIAC ALTERATIONS	Bejiqi et al. (2017)[21]; Shdaifat et al. (2017)[12]; Højland et al. (2018)[24].

Table 2 - Purpose of articles on secondary clinical manifestations and multidisciplinary aspects related to the Pierre Robin Sequence.

AUTHORS (YEAR)	TYPE OF STUDY	COUNTRY	LANGUAGE	TITLE	PURPOSE	CLASSIFICATION
Godbout et al. (2014)[1]	Case series	Canada	English	"Isolated Versus Pierre Robin Sequence Cleft Palates: Are They Different?"	Determine if there are dimensional differences between isolated cleft palate and cleft palate associated with the Pierre Robin Sequence (PRS).	Multidisciplinary aspects
van Nunen et al. (2014)[17]	Retrospective study	Netherlands	English	"Elevated infant mortality rate among Dutch oral cleft cases: a retrospective analysis from 1997 to 2011"	Assess the rate and cause of infant mortality in Dutch patients with isolated oral clefts or associated with other malformations, relating the different types of clefts to associated conditions or syndromes.	Multidisciplinary aspects
Andersson et al. (2015)[18]	Retrospective study	Norway	English	"Bilateral Hypodontia in Adolescents With Pierre Robin Sequence"	Evaluate the frequency of hypodontia and the pattern of involvement of this anomaly in the permanent dentition of children with PRS.	Secondary clinical manifestations
Basart et al. (2015)[2]	Cohort Study	Netherlands	English	"Etiology and Pathogenesis of Robin Sequence in a Large Dutch Cohort"	Analyze the diagnosis, investigate the etiology, and how pathogens attack the organism in PRS.	Multidisciplinary aspects
Filip et al. (2015)[3]	Retrospective study	Norway	English	"Multidisciplinary Aspects of 104 Patients With Pierre Robin Sequence"	Describe characteristics of patients in the Pierre Robin sequence with cleft palate, involving different specialties, to collect information on respiratory, growth, and feeding changes, assess the severity of the impairment and reparative treatments and investigate syndromes and associated genetic mutations, cognitive impairment, and psychological aspects.	Multidisciplinary aspects
Lind et al. (2015)[4]	Retrospective study	France	English	"Prenatal diagnosis of Pierre Robin Sequence: accuracy and ability to predict phenotype and functional severity"	Evaluate after birth the physical characteristics of fetuses, which showed signs suggestive of PRS on ultrasound exams.	Multidisciplinary aspects
Oliveira et al. (2015)[13]	Case report	Brazil	English	"Pierre Robin sequence: case report, the relevance of autopsy"	Report the orofacial clinical characteristics identified after the birth of the premature baby, and the identification of oropharyngeal malformation at autopsy, compatible with PRS diagnosis, which led to a cardiorespiratory arrest for preventing adequate treatment.	Multidisciplinary aspects
Rosa et al. (2015)[19]	Case report	Brazil	English	"Nager syndrome and Pierre Robin sequence"	Report a clinical case of a baby with Nager syndrome with the associated PRS triad.	Secondary clinical manifestations
Breugem et al. (2016)[5]	Literature review	Germany Australia Brazil Canada Scotland United States of America	English	"Best Practices for the Diagnosis and Evaluation of Infants With Robin Sequence: A Clinical Consensus Report"	Report a clinical consensus on the diagnosis and evaluation of children with RS, defined through the collaboration of a multicentric and multidisciplinary team to establish a starting point to define standards and treatment conducts.	Multidisciplinary aspects

		(USA) France Netherlands India England Japan Norway				
Faraz et al. (2016)[11]	Case report	Pakistan	English	“Pierre Robin Sequence: a rare presentation of absent Femur and inguinal hernia”	Report a case of PRS with unusual associated anomalies: the absence of femur and inguinal hernia.	Secondary clinical manifestations
Lambert et al. (2016)[15]	Case series	Canada	English	“Detailed Cleft Measurements: A Comparison Between Isolated Cleft Palates and Cleft Palates Associated with Cleft Lips”	Evaluate differences in the anatomical measurement of cleft lip and palate compared with cleft palate in patients without and with associated PRS.	Multidisciplinary aspects
Lopes et al. (2016)[20]	Retrospective study	Brazil	English	“Study of Genial Tubercles of Craniofacial Anomalies Individuals on Cone Beam Computed Tomography Scans”	Evaluate through Cone Beam Tomography the anatomical measurements and variations of the genial tubercle in patients with cleft lip and palate, isolated or associated with syndromes.	Secondary clinical manifestations
Trettene et al. (2016)[27]	Prospective study	Brazil	Portuguese	"Impact of promoting self-care on nursing workload"	Assess the impact of promoting self-care to caregivers of patients with PRS on the workload of the nursing team, responsible for supervising patients and providing guidance to those responsible.	Multidisciplinary aspects
Smalen et al. (2017)[22]	Retrospective study	Netherlands	English	“Permanent tooth agenesis in non-syndromic Robin sequence and cleft palate: prevalence and patterns ”	Compare the prevalence and pattern of dental agenesis between patients with PRS and patients with isolated cleft palate.	Secondary clinical manifestations
Bejiqi et al. (2017)[21]	Case report	Kosovo	English	“A Giant Heart Tumor in Neonate with Clinical Signs of Pierre - Robin Syndrome”	Report a case of a giant tumor in the left ventricle in a 3-week-old patient with PRS, and to investigate the clinical and morphological peculiarities of cardiac tumors in this age group.	Secondary clinical manifestations
Shdaifat et al. (2017)[12]	Case report	Jordan	English	“Identical twins with Pierre Robin syndrome; unusual encounter ”	Report a rare case of identical twin babies born with the complete Pierre Robin sequence.	Secondary clinical manifestations
Waldrop et al. (2017)[23]	Case report	USA	English	“Hypotonic newborn with cleft palate, micrognathia and bilateral club feet”	Report the investigation process of the diagnosis of a patient with isolated PRS associated with hypotonia.	Secondary clinical manifestations
Demoro et al. (2018)[28]	Experience report	Brazil	Portuguese	“Applicability of Orem: training the infant's caregiver with Robin Sequence”	Report the experience of nurses on the training of caregivers of infants with isolated PRS for maintenance of care after hospital discharge.	Multidisciplinary aspects
Højland et al. (2018)[24]	Case report	Denmark	English	"First reported adult patient with Tan ARP syndrome: A case	Report a clinical case of a 28-year-old patient with TARP Syndrome, which includes PRS, intellectual disability, and heart	Secondary clinical manifestations

				Report"	defects.	
Pinto et al. (2018)[25]	Retrospective study	Brazil	English	“Cephalometric Findings in Nine Individuals with Richieri-Costa-Pereira Syndrome”	Evaluate through cephalometric analyzes, the impairment of craniofacial development of patients with Richieri-Costa-Pereira Syndrome, and PRS.	Secondary clinical manifestations
Resnick et al. (2018)[6]	Retrospective study	USA	English	“Pathogenesis of Cleft Palate in Robin Sequence: Observations from Prenatal Magnetic Resonance Imaging”	Evaluate the association of tongue position in the intrauterine phase and the development of cleft palate between babies with and without PRS.	Multidisciplinary aspects
Souza et al. (2018)[14]	Prevalence study	Brazil	Portuguese	"Isolated Robin sequence: nursing diagnoses"	Evaluate the planning and implementation of systematic nursing care directed to infants with isolated PRS.	Multidisciplinary aspects
Do et al. (2019)[7]	Cohort Study	Canada	English	“Cleft Palates and Occlusal Outcomes in Pierre Robin Sequence”	Evaluate the association between the pattern of facial skeletal growth and dental occlusion with the size of the cleft palate in patients with PRS isolated or associated with syndromes.	Multidisciplinary aspects
Hsieh et al. (2019)[8]	Literature review	USA	English	"Pierre Robin Sequence"	Report clinical characteristics, diagnostic criteria, and multidisciplinary approaches to PRS.	Multidisciplinary aspects
Mateo-Castillo et al. (2019)[9]	Retrospective study	Brazil	English	“Novel dental phenotype in non-syndromic Pierre Robin Sequence: A retrospective study”	Compare the prevalence of dental malformations, such as taurodontism, root laceration, agenesis, and tooth transposition, among patients with PRS, patients with isolated cleft palate, and patients without craniofacial anomalies.	Secondary clinical manifestations
Robbins et al. (2019)[16]	Case report	USA	English	“Combined Tongue-Palate Fusion With Alveolar Bands in a Patient With Pierre Robin Sequence and Van der Woude Syndrome”	Report a clinical case of a baby who presented PRS associated with Van der Woude Syndrome with tongue adhesion in the cleft palate.	Secondary clinical manifestations
Rojare et al. (2019)[26]	Case report	France	English	“The Smith-Lemli-Opitz Syndrome and Dentofacial Anomalies Diagnostic: Case Reports and Literature Review”	Present the general clinical and oral maxillofacial characteristics of the Smith-Lemli-Opitz Syndrome, including PRS and dental anomalies, such as hyperdontia, oligodontia, enamel development defects, and early tooth eruption.	Secondary clinical manifestations
Cleary et al. (2020)[10]	Case-control study	Germany Croatia Malta Netherlands Ireland Italy Norway Spain Wales Portugal Switzerland	English	"Methadone, Pierre Robin sequence and other congenital anomalies: case – control study	Evaluate the relationship between the use of Methadone and the devlopment of PRS.	Multidisciplinary aspects

Discussion

Different theories explain the etiology of mandibular hypoplasia, which triggers other changes in PRS[5,6], such as the theory of intrauterine mechanical compression of the mandible, which affects mandibular growth; the theory of psychomotor development, in which the degenerative loss of motor control of the muscles results in mandibular hypoplasia; and varied genetic theories[6,13]. The investigation of the etiology and definition of the diagnosis are complex processes, involving clinical evaluation and complementary, imaging, and laboratory tests[5,8,10].

In general, the diagnosis of PRS is defined by the presence of micrognathia, glossoptosis, and airway obstruction, being the presence of cleft a very common complementary characteristic[1,3,5,7,8,15]. In the case reports found in this review, all children had cleft palate[11-13,16,19,21,23]. The cases presented by Bejiqi et al. (2017)[21], Waldrop et al. (2017)[23] and Robbins et al. (2019)[16] showed wide clefts, which were related to severe respiratory distress. Godbout et al. (2014)[1] compared the dimensions of cleft palate between patients with PRS and patients with isolated cleft palate and concluded that patients with PRS have wider cleft palate, both in the hard and soft palate than patients with isolated cleft. Also, according to Do et al. (2019)[7], the larger the size of the cleft palate, the greater the degree of mandibular retrusion.

Syndromes and genetic disorders associated with PRS may be present at birth or manifest with late-onset[5]. Lind et al. (2015)[4] evaluated the postnatal physical characteristics of fetuses showing signs suggestive of PRS on ultrasound examinations, and found that most of the evaluated babies had chromosomal aberrations or neurological abnormalities, not exclusively related to PRS. Only a minority of cases of fetal retrognathia were related to complete PRS, concluding that it is not possible to predict the functional severity of isolated PRS in the prenatal phase. Besides that, PRS malformations can not be identified in ultrasound exams[13].

The genetic investigation should be done with caution, because phenotypic changes are not always related to syndromes[6]. Waldrop et al. (2017)[23], reported a thorough investigation of a child with hypotonia and significant respiratory problems, who was diagnosed with a specific type of myopathy associated with PRS, emphasizing the need to always consider other possible etiologies, in addition to syndromic conditions. However, the possible change in diagnosis during growth or the possibility of clinical availability of genetic sequencing technology was highlighted. Basart et al. (2015)[2] confirmed the occurrence of a high rate of changes in the diagnosis of isolated PRS to PRS associated with chromosomal abnormalities, due to the late finding of associated abnormalities, which were generally not detected or there was great difficulty to be detected in childhood. Therefore, it is suggested that the follow-up and reassessment of babies with SPR over a prolonged period is essential to complete the diagnosis.

Despite the defined clinical presentation, the pathogenesis of PRS is not well established[2,6]. The aggression mechanisms of its etiopathogenic agents against the organism remain uncertain, however, connective tissue dysplasia, such as Stickler's syndrome, intellectual disability, and multisystemic disorders were common findings in patients with non-isolated PRS[2]. In the selected studies of this review, besides the Stickler Syndrome[1-9,12,13,19,21,23,25], the following conditions were also cited: Treacher Collins Syndrome[8,12,20,21]; Velocardiofacial[8,13,19,21]; Fetal alcohol[8,13,21]; Nager [8,19]; Wagner[12]; Camera-Marugo-Cohen[23]; TARP[24]; Richieri-Costa-Pereira[25]; Smith-Lemli-Opitz[26]; van der Woude[16]; among others[8,21,23].

The occurrence of deaths in patients with PRS is related to severe respiratory complications, as a result of the existing abnormalities[8,13,17,19]. In the cases reported by Oliveira et al. (2015)[13] and Rosa et al. (2015)[19], the babies, with isolated PRS and associated Nager syndrome, respectively, died from cardiorespiratory arrest.

Among the secondary clinical manifestations found in patients with PRS are dental anomalies[9,18,22,26], bone and muscle[11,16,19,20,23,25], and cardiac alterations[12,21,24]. Dental anomalies are common findings in patients with cleft lip and palate: Anderson et al. (2015)[18], Smalen et al. (2017)[22] and Mateo-Castillo et al. (2019)[9], found a high prevalence of dental agenesis in children with PRS. In these studies, this anomaly affected mainly bilateral lower premolars, suggesting that changes in the development of the mandible, and consequent loss of space, may be precursors to the occurrence of dental agenesis[22]. Mandibular hypoplasia in patients with PRS can be a consequence of intrauterine compression of the mandible, defects in the origin and growth of Meckel's cartilage, as well as muscle defects with improper tongue position[6,13,16,22]. Cardiac changes can range from reversible deformities[12,24] to serious diseases[21]. And bone and muscle involvement are not necessarily related to syndromes[11,20,23].

Filip et al. (2015)[3] evaluated the multidisciplinary care required by patients with PRS, due to cognitive and psychological impairment, speech and breathing difficulties, growth and feeding problems, the severity of the cleft palate, necessary surgical treatments, the occurrence of oronasal fistulas, as well as, syndromes and genetic mutations. Thus, the need for permanent multidisciplinary assistance for this patient is evident, composed of pediatricians, geneticists, plastic surgeons, otolaryngologists, psychologists, speech therapists, nurses, and dental professionals, such as pediatric dentists, orthodontists, and oral and maxillofacial surgeons[2,3,5,8]. Breugem et al. (2016)[5], through a consensus by professionals from different countries, reinforced the idea that multidisciplinary collaboration is essential for the progress of care and the promotion of well-being for patients with PRS, due to the complexity and factors associated with this condition.

The first years of life require special attention, as the nursing babies routinely needs to control respiratory changes and manage feeding difficulties. In addition to carrying out baby care in the hospital, the nursing team has the responsibility to provide training to caregivers so that they can maintain the necessary care after hospital discharge. The training of caregivers by the nursing team promotes the strengthening of the trinomial caregiver-patient-family, decreases the costs of the health system, since it favors hospital discharge, and consequently, the risk of hospital infection; as well as, improves the prognosis and quality of life of these babies. For the patient to be discharged, in addition to clinical conditions and medical advice, the caregiver of babies with PRS should be considered able to provide care to infants with this PRS[14,27,28].

In this integrative review, it was found that the most common type of study in journals, about the topics investigated, was report or series of cases, corresponding to approximately 39.3% of the studies[1,11-13,15,16,19,21,23,24,26] included in the final analysis. While 7.14% of the articles[2,7] included followed a cohort design. Within the context of Evidence-Based Practice[29,30], the scarcity of studies with a higher level of scientific evidence, such as randomized clinical trials, shows the need for future investigations to improve care for patients with PRS. However, in the absence of strong evidence in the current scenario, literature

reviews, case discussions, reports of experts' experiences, as well as observational studies must be appreciated.

Conclusion

The multidisciplinary aspects related to PRS showed the complexity of the diagnosis and etiopathogenesis of this disorder, the higher risk of mortality and wider cleft palates in affected individuals, as well as the need to promote self-care to parents of babies with PRS to reduce the risks of complications and improve quality of life of these patients. Whilst dental and/or bone, muscle, and cardiac malformations, characterized as secondary clinical manifestations of PRS, may feature an isolated factor or a syndromic condition.

Acknowledgements: The authors would like to thank the financial support granted by the National Council for Scientific and Technological Development (CNPq - PIBIC nº 156686 2019-8).

Conflict of interests: The authors declare no conflict of interest.

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Como citar este artigo:

Miranda-Filho AEF, Oliveira LMMO, Camargo MOL, Rodrigues HSG, Tamburini ABF, Pereira MSS, Baldim AA, Marques NCT. Multidisciplinary aspects and secondary clinical manifestations of Pierre Robin sequence: an integrative review. Rev. Aten. Saúde. 2020; 18(6): 301-313.