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Pierre Robin sequence: Management of respiratory and feeding complications during the first year of life in a tertiary referral centre

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ABSTRACT

Objectives: To review early clinical manifestations of Pierre Robin sequence (PRS) and their management during the first year of life in the University Hospitals Leuven.
Methods: Retrospective series of 48 patients with PRS born between 2001 and 2011 and treated at a tertiary referral hospital. Review of the current literature about management of respiratory and breathing difficulties in the early life of PRS patients.
Results: Of our cleft palate patients 15.3% presented with PRS. A syndrome was diagnosed in 14.6%, associated anomalies without a syndromic diagnosis in 56.3% and isolated PRS in 29.2% of the cases. Mortality rate directly related to PRS was 2.1%. Respiratory difficulties were observed in 83.3% and feeding difficulties in 95.6% of the patients. Respiratory problems were addressed in a conservative way in 75%, in a non-surgical invasive way in 42.5% and in a surgical way in 12.5%. A statistically significant relationship between the association of a syndrome or other anomalies, and a higher need for resuscitation and invasive treatment were found (chi-square test, p-values = 0.019 and 0.034). Feeding difficulties were managed conservatively in 91.3%, invasively in 80.4% and surgically in 15.2%.
Conclusions: PRS is frequently associated with other abnormalities or syndromes. Therefore routine screening for associated anomalies in neonates with PRS is recommendable. Respiratory and feeding complications are highly frequent and possibly severe, particularly in patients with associated anomalies or syndromes, and should be recognized and addressed appropriately in an early stage. There is a potential role for the nasopharyngeal airway in reducing the need for the more traditional surgical interventions for respiratory problems.

1. Introduction

Pierre Robin sequence (PRS) is described as the triad of micrognathia, glossoptosis and cleft palate (CP). Some authors prefer the original diagnostic criteria stated by Pierre Robin in 1923: respiratory obstruction, micrognathia and glossoptosis [1–3].

PRS is not a syndrome, but a sequence in which a single primary anomaly leads to multiple secondary anomalies. The primary structural abnormality in the sequence of PRS is believed to be the deficient outgrowth of the mandible before the embryological age of 9 weeks, which reduces the oropharyngeal space. The secondary defects, glossoptosis and cleft palate, are caused by the upward and posterior displacement of the tongue, due to the reduced oropharyngeal space, resulting in a mechanical impairment of fusion of the palatal shelves [4,5]. The SOX9 gene, a critical chondrogenic regulator, has been linked to non-syndromic isolated PRS [6]. This substantiates the hypothesis that mandibular outgrowth is the primary defect in the sequence, as the mandibular development depends on Meckel's cartilage. Dysfunction of the orofacial musculature is an alternative hypothesis stated in the pathogenesis of PRS [4].

The incidence of PRS varies between 1 in 8500 and 1 in 14 000 living births [7,8]. PRS can be isolated (iPRS), it can be

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associated with an identifiable syndrome (sPRS) or it can be associated with other anomalies without a syndromic diagnosis (aPRS). The syndromes most frequently associated with PRS are Stickler syndrome (SS), 22q11.2 deletion syndrome or velocardiofacial syndrome and Treacher Collins syndrome [9].

After birth PRS patients can present with important breathing and feeding difficulties secondary to the triad of birth anomalies of variable degree of severity.

Feeding and growth issues can be secondary to the respiratory problems, but they also can be due to swallowing dysfunction, aspiration, and gastro-esophageal reflux disease (GERD). Another portion of the feeding problems is caused by the underlying syndrome or associated anomalies. A combination of these factors may result in failure to thrive [2,3].

Which treatment modality to use as first-line intervention for respiratory issues is controversial. Various methods for management of respiratory difficulties are being applied, ranging from prone positioning, nasopharyngeal airway (NPA), prolonged endotracheal intubation (ETI), positive airway pressure ventilation, to surgical intervention. The most widely adapted surgical techniques include glossopexy, mandibular distraction osteogenesis (MDO) and tracheotomy [2,3,5].

In the management of feeding issues, the options consist of oral feeding techniques, use of a Special Needs Feeder, formerly known as the Habermann feeder, a palatal plate which seals the CP and ensures the creating of a vacuum during suction, high calorie or thickened nutrition, placement of a nasogastric feeding tube (NGT) or a gastrostomy [2].

This study aims (I) to document the prevalence of sPRS, aPRS and iPRS and the prevalence of PRS within our CP population, (II) to determine the prevalence of comorbidities such as breathing and feeding difficulties within the first year of life, and their management, and (III) to search for differences in incidence of complications and interventions between the iPRS, sPRS and aPRS groups and compare the results to the current literature.

2. Methods

In this retrospective analysis all patients born between 2001 and 2011 diagnosed with PRS and admitted to the University Hospitals Leuven or diagnosed with PRS in a referring hospital and afterwards admitted to the University Hospitals Leuven were identified. This was done by means of a search of the Leuven Multidisciplinary Cleft database, identifying 48 PRS patients and 314 CP patients over an 11 year period. Subsequently, the medical records of the PRS patients were retrospectively analyzed. The following information was collected for each patient: clinical features at birth, hospitalizations during the first year of life, mortality, respiratory and feeding difficulties and their management, diagnostic investigations and follow-up. The data were analyzed using IBM SPSS version 20. To compare respiratory and feeding complications and treatment modalities between the subgroups the chi-square test and Fisher's exact test were used. Finally, a literature search using PubMed was performed, using the MeSH term Pierre Robin sequence, to summarize the current knowledge about PRS, with special attention to the management of respiratory and feeding difficulties during the first year of life.

3. Results

3.1. Demographics

The proportion of the CP patients diagnosed with PRS was 15.3%. In 5 of the 48 cases of PRS, the diagnosis was dubious because of the absence of CP. Nevertheless, they were enrolled in the study, as their diagnosis was made by a clinician. Micrognathia and glossoptosis were observed in respectively 100 and 87.5% of the patients.

Table 1
Primary diagnosis.

	Number	Percentage
Total patients	48	100
Non-syndromic PRS	41	85.4
iPRS	14	29.2
aPRS	27	56.3
sPRS	7	14.6
Stickler syndrome	4	8.3
Stickler syndrome and Hurler syndrome	1	2.1
CHARGE syndrome	1	2.1
Kabuki make up syndrome	1	2.1

iPRS: isolated Pierre Robin sequence; aPRS: Pierre Robin sequence with associated anomalies without syndromic diagnosis; sPRS, syndromic Pierre Robin sequence.

The subdivision of the PRS population in 3 groups is summarized in Table 1. Based on genetic testing and evaluation by a geneticist 7 patients (14.6%) were classified sPRS. SS was the most commonly associated syndrome.

3.2. Management during the first year of life

3.2.1. Mortality

Of the total number of PRS patients, 5 patients (10.4%) died, 4 of them dying before the age of 6 months. The cause of death of 1 patient was related to PRS, as the patient died from upper airway obstruction. The remaining 4 patients died due to sepsis or associated severe cardiac or neurologic anomalies.

3.2.2. Hospitalization

A hospitalization at the neonatal care unit, instead of the usual stay with the mother on the maternity unit, was documented in 87.5% of the patients with an average length of stay of 27 days (range 1 to 83 days). Hospitalization of patients in their first year of life occurred 2.23 times on average, ranging from 0 to 7 times. The mean total length of these hospital stays was 33 days (range 0 to 83 days).

3.2.3. Respiratory difficulties

As displayed in Table 2, 40 patients (83.3%) suffered from respiratory difficulties at some stage. The respiratory difficulties

Table 2
Presentations of respiratory and feeding difficulties.

	Number	% Of patients with RD ($n=40$) or FD ($n=46$)	% Of all patients ($n=48$)
RD	40	100	83.3
Upper airway obstruction	35	87.5	72.9
Respiratory infection	18	45.0	37.5
Cardiovascular system	10	25.0	20.8
Clinical aspiration	7	17.5	14.6
Central nervous system	1	2.5	2.1
Lower airway obstruction	1	2.5	2.1
FD	46	100	95.8
Intake problems	20	43.5	41.7
GERD	14	30.4	29.2
RD during feeding	10	21.7	20.8
FTT	9	19.6	18.8
Proven aspiration	4	8.7	8.3
Vomiting	4	8.7	8.3
Food allergy	1	2.2	2.1

RD, respiratory difficulties; FD, feeding difficulties; GERD, gastro-esophageal reflux disease; FTT, failure to thrive.