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Review Article

Pierre Robin sequence: Review of diagnostic and treatment challenges

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ABSTRACT

Pierre Robin sequence is not a rare condition and paediatric specialists caring for respiratory related issues are likely to encounter cases in their practice. There have been a few recent reviews on the topic, mostly focusing on the surgical interventions performed for cases with severe airway obstruction. In the present review, we will highlight the different challenges that remain today in the global evaluation of infants afflicted with this condition through a thorough review of the medical literature, giving the clinician a full scope of the disease and of the various management options. The need for an improved objective evaluation of airway obstruction and for a better classification will be emphasized. We are therefore proposing a novel classification scheme that will better account for respiratory and feeding difficulties in these infants. Finally, many knowledge gaps persist regarding this condition, underlining the necessity for further research both in the genetic field and regarding the outcome of therapy.

Contents

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1. Introduction

Pierre Robin sequence (PRS) refers to the association of micrognathia, glossoptosis, and airway obstruction. Typically, a wide U-shaped cleft palate is also associated with PRS; in large series, a cleft palate is reported in up to 73–90% of cases [1–5]. Descriptions of cases of micrognathia and cleft palate have been published since the 19th century in the English medical literature (reviewed in Randall et al. [6]). Pierre Robin first described the treatment of mandibular hypoplasia both in children and in adults in 1923 [7] in the French medical literature but his first description of the condition that now bears his name was not published until 1934 [8].

The incidence of PRS, derived from population-based studies, varies from country to country with the highest incidence in the United States with one case/3120 live births (one case/5480 live births for isolated Pierre Robin sequence, derived from a survey involving 44 states) [9]. In other countries, the incidence varies from one case/8060 live births in Germany [10], to one case/8500 in the UK [11], to one case/14,000 in Denmark [12]. These variations might be explained by the fact that the data was collected at different time periods over five decades and different methods were utilized.

Other anomalies are associated with PRS and may appear in conjunction with a recognized syndrome. From large series, it is reported that approximately 50% of PRS cases are syndromic [1,13,14] and the three most common syndromes (accounting for 65% of the syndromic cases) are Stickler (the most frequent), velocardiofacial and Treacher-Collins [1,13–18]. In a recent comprehensive review by Tan et al. [19], more than 50 syndromes have been described in association with PRS.

Mortality rates for PRS have been published from various countries (Canada [1], United Kingdom [11], Unites States [5] and The Netherlands [20]) over time. It was found to lie between 3.6% and 21%. Infants with associated anomalies or syndromic cases have a higher mortality. In the most recent study published from a group in the United States (data from 2001 to 2012, 181 infants, average follow-up 35 months) [5], the overall mortality rate was 16.6% with no mortality in isolated PRS. Infants with cardiac or central nervous system anomalies had the highest mortality (respectively 39% and 33%).

2. Pathophysiology

The exact cause and the pathophysiology of Pierre Robin sequence are still unknown despite significant progress in the last decade. SOX9 gene, a critical chondrogenic regulator, has been linked to nonsyndromic PRS in families with more than one member affected [21]. Furthermore, more recent work has shown that multiple non-coding elements contribute to the craniofacial regulation of SOX9 expression; in PRS, these craniofacial regulatory elements are the site of deletions, contributing to the typical phenotype [22].

The most frequent syndromic PRS patients have different genes involved: Stickler syndrome is associated with mutations in COL genes (COL2A1, COL9A1, COL11A1, and COL11A2, reviewed by Acke et al. [23]); velocardiofacial syndrome arises from a microdeletion of chromosome 22q11.2 [24]; and Treacher Collins syndrome is associated with mutations in the TCOF1, PLOR1C, and POLR1D genes [24–26].

There are three major hypotheses to explain the sequence of events in PRS [19]: (a) hypoplastic mandible; (b) oropharyngeal and muscular deficiencies; (c) compression of the mandible in utero. The hypoplastic mandible theory is the one mostly retained in the literature and the one that has been demonstrated in animal models (mostly murine) [27–29]. The primary defect is thought to be in Meckel's cartilage, the embryonic structure involved in the formation and growth of the mandible. The subsequent mandibular hypoplasia is thought to lead to a small mouth volume, abnormal position of the tongue, and the secondary impairment of palatal closure [30].

In the oropharyngeal and muscular deficiency hypothesis, it is believed that hypotonia of the oropharyngeal muscles could result in hypoplasia of the mandible (reviewed in Tan et al. [19,31]). The persistence of feeding issues for weeks to months in infants afflicted with PRS in which respiratory compromise has resolved suggests anomalies in pharyngeal tone and motility. Foetal oral muscular activity, including swallowing movements, is thought to be required for normal growth of the mandible. Interestingly, many conditions characterized by hypotonia are also associated with PRS (congenital myotonic dystrophy, for instance).

Finally, the mandible compression theory probably plays a role in a small proportion of infants born with PRS, in particular those having experienced a pregnancy associated with foetal constraint