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REVIEW

Isolated Robin sequence in siblings: Review of current concepts☆

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Summary Robin sequence is a condition that includes the triad of micrognathia, glossoptosis and upper airway obstruction, although many authors now consider that cleft palate is also an important part of the sequence. It can be classified as isolated, syndromic or associated with other anomalies without an identifiable syndrome. A possible genetic cause for isolated Robin sequence is yet under preliminary investigation, and the finding of siblings with the same condition, as are the two children we present in this work, is extremely rare, with only nine similar cases previously described. Our article includes the description of the treatment plan and outcome for both children. We review the current concepts and trends of epidemiology, genetics, diagnosis and different treatment options available. We conclude that in cases of failure of more conservative measures in the first weeks, mandibular distraction osteogenesis may be a good and rational option for the management of isolated Robin sequence, as is currently supported in recent literature, providing a reliable way of avoiding tracheostomy.

Introduction

Robin sequence (RS), first described by Pierre Robin in 1923[1] (formerly known as Pierre Robin syndrome), is a condition that includes the triad of micrognathia, glossoptosis and upper airway obstruction, although many authors now consider that cleft palate, which can be U- or V-shaped, is also an important part of the sequence. The reported incidence ranges from 1:8500[2] to 1:14,000,[3] with a male to female ratio of 1:1 and an overall mortality rate

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that has been declining in the last decades due to better treatment options (now averaging 3%).

Current concepts

We can classify this pathology in three categories. Based on Holder-Espinasse et al.,[4] Evans et al.[5] and Bütow et al.,[6] who published three of the largest studies to date, isolated RS, which implies that there is no other anomaly present, corresponds to approximately half of the cases (48–66%). Another group includes cases of RS with associated anomalies but no identifiable syndrome (9–17%). The third category, which has the worse prognosis, is syndromic RS (18–35%). Stickler syndrome is by far the most frequent in the latter group, but many others exist, such as velocardiofacial syndrome, Treacher–Collins syndrome, Nager syndrome or hemifacial microssomia.[7]

We can also classify RS by severity. Although there are several classifications available, we use one that is stratified in three groups, suggested by Caouette-Laberge, as it is simple and therapeutically oriented. The milder cases, group I, have adequate respiration in prone positioning, and can be fed regularly. In group II, there is difficulty in feeding, with need of gavage. In the most severe cases, group III, there is the need for both endotracheal intubation and gavage.[8]

Concerning epidemiology and genetics, there are many chromosomal anomalies related to RS associated with other anomalies or a syndrome: dup 2q13-21; dup 1q23.1-q31.1; del 2q33.1-33.3; del 2q32.3-q33.2; del 4qter; del 11q; del 14q; del 16q; del 22q11; trisomy 3q2; monosomy Xp.[7,9] However, in isolated RS, none were identified, which leaves the question of a possible environmental cause in some of these cases, like intrauterine compression, or if there are other gene mutations that have not yet been identified. Some authors believe there may be an influence of intrauterine exposure to teratogens. There are currently some genes being investigated, especially SOX9, but still no definitive conclusion has been achieved.[10,11] Isolated RS has a 9–16%[4,12] chance of twinning, versus the normal population average of 1%. Thirteen percent of cases have a family history of RS[4] and 13–27% have relatives with a cleft lip or palate.[7,13] We found only nine cases of siblings in the English literature.[4,14–17]

Prenatal diagnosis may be possible if micrognathia is detected with ultrasound, although it is only suspected in 7% of cases. Beyond standard monitoring with pulse oximeter, polysomnography and fibre optic endoscopy are performed in many centres. Determining if airway obstruction is merely due to glossoptosis is an important step in diagnosis; other causes may need further treatment or tracheostomy. Imaging studies, like computed tomography (CT) scans (with 3D reconstruction), may provide additional information, such as maxillary–mandibular discrepancy and tooth-bud positioning.

The treatment guidelines vary between institutions, especially concerning timings and options offered to the patient and parents. At present, the main options are prone positioning, nasopharyngeal tube (NPT), tongue–lip adhesion, mandibular distraction and tracheostomy. Prone positioning is only adequate for group I patients. It is a non-invasive treatment modality that is adequate in 61–75% of cases,[18–20] although it needs adequate monitoring for a period of several months.[18] An NPT is used when positioning does not relieve upper airway obstruction, and is effective in 60–82%[20,21] of the remaining cases of isolated RS. Being non-invasive, the long-term complications of NPT are very low. On the other hand, the treatment duration can be quite long, with reported means of 2[22]–8 months.[21] Kochel et al.[23] and Li et al.[18] point out that although this is a simple method, the risk of the tube changing its position is real, with relapse of the airway obstruction; therefore, there are those that advocate using this modality only for short periods if the respiratory insufficiency is severe.[24] Moreover, Jarrahy[25] states that management with NPT is contraindicated if loss or malposition of the tube results in an immediate symptomatic change in the airflow pattern indicative of either partial or total obstruction: "use of the NPT in this setting can set the stage for catastrophic events". Nevertheless, there are now protocols to allow early hospital discharge (2 weeks after birth) and teach parents how to take care of children with an NPT and adequate monitoring at home, with proven results.[21,22,26]

Some authors state there is an indication for surgery when the maxillary–mandibular discrepancy is larger than 8–10 mm. Others consider the need to operate when conditions are not optimal to discharge an infant with an NPT, for example, when parents cannot cope with home monitoring. There is also a small number of patients in which NPT is not effective, and upper airway obstruction episodes (although less) continue to exist. In a survey of members of the American Cleft Palate-Craniofacial Association, Collins et al.[27] showed that currently the majority of surgeons choose to perform surgical treatment on their RS patients within the first month of age (61%, $n = 51$), and that mandibular distraction osteogenesis (MDO) was the preferred surgical option (48%, $n = 40$), with tongue–lip adhesion (TLA) and tracheostomy taking second and third place, respectively (23%, 14%).

Tongue–lip adhesion is adequate for group II and some group III cases, but has a considerable rate of complications, like dehiscence and aspiration. Probably its greatest advantage is the ability to be reversible without major sequelae. Nevertheless, it is nowadays being replaced[27] by a less conservative approach, mandibular distraction osteogenesis, that has more than 80–90% of success in reverting airway obstruction and avoiding tracheostomy,[28,29] and also more than 80% success in nulling feeding difficulties within weeks.[30] Flores et al.[26] recently published a review in which early MDO fared better against tongue–lip adhesion, with higher oxygen saturations, lower apnoea–hypopnoea index and lower incidence of tracheostomy. Papoff et al.[31] also found greater medium-term benefits using MDO rather than TLA (more stable breathing and more rapid improvement in oral feeding), although TLA achieved better outcomes than MDO in the short term, allowing for earlier extubation. Patients who most benefit from this treatment option are those in group III, but also group II patients with weight gain of less than 700 g in the first 4 weeks of life and dependence on an NPT for airway management. Together, these two parameters predict an extended hospital stay of greater than 100 days if a protocol for early home discharge is not established.[19] We