Pierre Robin Sequence

Contents

Pierre Robin described a group of patients with cleft palate, micrognathia, and glossoptosis in *1923* (Robin 1923). The meticulous documentation of the triad of findings led to the recognition of the sequence that bears his name (Randall et al. 1965). Pierre Robin sequence is estimated to affect approximately 1 in 8,500 births (Bush and Williams 1983).

Synonyms and Related Disorders

Glossoptosis, micrognathia, and cleft palate; Pierre Robin syndrome (PRS); Robin anomalad

Genetics/Basic Defects

1. Inheritance
    1. Sporadic in most instances
    2. Rare occurrence of isolated robin sequence in siblings: rare (da Costa and Matias 2014)
    3. May be familial with autosomal dominant mode of inheritance (Sidhu and Deshmukh 1989)
    4. Robin anomalad: its nonspecificity and associated syndromes (Cohen 1976)
    5. Syndromic form: etiologically heterogeneous (Shprintzen 1988, 1992; Cohen 1999; Holder-Espinasse et al. 2001; Taylor 2001; Evans et al. 2011; Buchanan et al. 2014)
        1. Monogenic
            1. Stickler syndrome (common cause) (Sheffield et al. 1987; van den Elzen et al. 2001): associated with mutations in COL genes (*COL2A1*, *COL9A1*, *COL11A1*, and *COL11A2*) (Acke et al. 2012)
            2. Velocardiofacial syndrome (microdeletion of chromosome 22q11.2)
            3. Beckwith-Wiedemann syndrome
            4. Camptomelic syndrome
            5. Cerebrocostomandibular syndrome
            6. Congenital myotonic dystrophy
            7. Larsen syndrome
            8. Mandibulofacial dysostosis
            9. Miller-Dieker syndrome
            10. Nager syndrome (Rosa et al. 2015)
            11. Otopalatodigital syndrome II
            12. Popliteal pterygium syndrome
            13. Robin-oligodactyly syndrome
            14. Spondyloepiphyseal dysplasia
            15. Treacher Collins syndrome associated with mutations in the *TCOF1*,

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_192

PLORIC, and *POLRID* genes (Kadakia et al. 2014)
   2. Chromosomal
      1. Del(22q) velocardiofacial syndrome (common cause)
      2. Del(4q32-qter) syndrome
      3. Del(2q24-q22) syndrome
      4. Del(6q) syndrome
      5. Dup(11q21-q23) syndrome
      6. 17q21 deletion/translocation near SOX9
   3. Teratogenic
      1. Fetal alcohol syndrome
      2. Fetal hydantoin syndrome
      3. Fetal trimethadione syndrome
      4. Maternal diabetes
   4. Deformation
      1. Oligohydramnios
      2. Uterine structural anomalies
      3. Amniotic band syndrome
   5. Disruption: amniotic band disruption
   6. Unknown cause:
      1. CHARGE syndrome
      2. Femoral dysgenesis
      3. Moebius sequence
      4. Robin/amelia association
      5. Distal arthrogryposis-Robin syndrome
2. Pathogenetically and phenotypically variable (Robin sequences and complexes) (Carey et al. 1982)
   1. Malformation sequence based on intrinsic mandibular hypoplasia that prevents the normal descent of the tongue interfering with palatal fusion, for example:
      1. Treacher Collins syndrome
      2. Del(22q) syndrome
   2. Deformation sequence based on extrinsic mandibular hypoplasia caused by intrauterine constraint
      1. Oligohydramnios (reduced amniotic fluid results in compression of the chin against the sternum restricting mandibular growth and impacting the tongue between the palatal shelves)
      2. Mandibular catch-up growth expected after birth when intrauterine deforming forces are no longer acting since micrognathia is based upon intrauterine molding
      3. Neurogenic hypotonia leading to lack of mandibular exercise
      4. Connective tissue dysplasia: Stickler dysplasia complex
      5. Spondyloepiphyseal dysplasia congenita complex
3. Genetic basis of the Pierre Robin sequence (Jakobsen et al. 2006)
   1. A comparison among cases in the literature and cases in cytogenetic databases revealed consistency to a certain degree to loci 2q24.1-33.3, 4q32-qter, 11q21-23.1, and 17q21-24.3.
   2. No particular candidate genes can be identified for certain from the present study, but GAD67 on 2q31, PVRL1 on 11q23-q24, and the SOX9 gene on 17q24.3-q25.1 are suggested to be important.

Clinical Features

1. Classic triads
   1. Posterior, U-shaped cleft palate
   2. Micrognathia/retrognathia
   3. Glossoptosis (observed tendency of the tongue to move posteriorly obstructing the oropharynx)
2. Pierre Robin sequence using different criteria
   1. Mandibular deficiency
   2. Cleft palate (U-shaped) (Hanson and Smith 1975)
   3. Upper airway obstruction
3. Respiratory difficulty
   1. Often the first sign causing concern relating to feeding
   2. May not necessarily be present at birth
   3. Upper airway obstruction and apnea
      1. Glossoptosis associated with retrognathia
      2. Upper airway collapse secondary to:
         1. Hypotonic pharynx
         2. Laryngomalacia
         3. Laryngeal cleft
         4. Laryngeal web

4. Complications of continuing airway obstruction
    1. Failure to thrive
    2. Pectus excavatum
    3. Decreased pulmonary function
    4. Sudden death
4. Failure to thrive
5. Developmental delay
    1. Usually not present in isolated Robin sequence
    2. May be present depending on the underlying syndrome
6. Middle ear diseases associated with cleft palate
    1. Otitis media (80%)
    2. Auricular anomalies (75%)
    3. Hearing loss, mostly conductive (60%)
7. Cleft palate-associated problems (Williams et al. 1981)
    1. Speech defects (severe nasal escape of air)
    2. Abnormal articulation
    3. Velopharyngeal insufficiency
8. "Catch-up growth" of the mandible
    1. Normal mandibular growth in patients with Robin sequence secondary to mechanical constraint
    2. Deficient mandibular growth in patients with intrinsic mandibular anomalies
9. Other signs and symptoms and associated anomalies depending on the underlying conditions

Diagnostic Investigations

1. Assess respiratory sounds with stethoscope during feeding and at rest.
2. Monitor developmental milestone achievement.
3. Pulse oximetry monitoring to document drops in oxygen saturation.
4. Flexible fiber optic nasopharyngoscopy.
    1. To identify exact mechanism of upper airway obstruction.
    2. To assess pharyngeal, palatal, lingual, and laryngeal morphology and function during feeding and swallowing
5. Identify the underlying cause of the micrognathia.
6. Orthodontic assessment.
7. Hearing assessment.
8. Polysomnography, polygraphy, and oximetry (Breugem et al. 2016).
    1. Polysomnography or polygraphy can quantify airway obstruction and identify comorbidities, such as central apnea (DeHaan et al. 2015).
    2. Oximetry may be specific for detecting obstructive sleep apnea (OSA), but it is not sensitive for detecting airway obstruction and OSA (Marcus et al. 2012).
9. Cervical spine evaluation to rule out cervical instability, especially those with suspected abnormalities in bone or collagen formation (Barr et al. 2016).
10. Cephalometric radiographs
    1. Deformation sequence
        1. Mandible
            1. Short body
            2. Short ramus
            3. Increased gonial angle
            4. Incomplete catch-up growth
        2. Cranial base angle: decreased
    2. Treacher Collins syndrome
        1. Mandible
            1. Short body
            2. Short ramus
            3. Characteristic shape
            4. Severely affected growth
        2. Cranial base angle: decreased
    3. Del(22q11.2) syndrome
        1. Mandible
            1. Retrognathia
            2. Essentially normal in shape
        2. Cranial base angle: increased
    4. Stickler dysplasia complex
        1. Mandible
            1. Short ramus
            2. Antegonial notching of body
        2. Cranial base angle: decreased
    5. Spondyloepiphyseal dysplasia congenita complex: short body of mandible
11. Chromosome analysis: del(22q11.2) and others.
12. Molecular diagnosis (Cohen 1999).
    1. Treacher Collins syndrome: mutations in *TCOF1*

2. Stickler dysplasia complex
   1. Mutations in *COL2A1*
   2. Mutations in *COL11A1*
3. Spondyloepiphyseal dysplasia congenita complex: mutations in *COL2A1*

Genetic Counseling

1. Recurrence risk
   1. Patient's sib: rare unless Pierre Robin sequence is a part of a syndrome
   2. Patient's offspring: rare unless Pierre Robin sequence is a part of a syndrome
2. Prenatal diagnosis (Hsieh et al. 1999)
   1. Ultrasonography (Pilu et al. 1986)
      1. Polyhydramnios
      2. Micrognathia/retrognathia and cleft palate
      3. Cardiac anomalies
   2. Chromosome analysis: occasional (trisomy 21, 18)
3. Management (Shprintzen 2001; Evans et al. 2011)
   1. Prone positioning of infants (Tewfik et al. 2015) believed to help prevent the tongue and mandible from obstructing the airway, leading to generally improved oxygen saturation
   2. Nasogastric tube placement for early feeding and ensuring adequate relief of the airway obstruction (Heaf et al. 1982)
   3. Occupational therapy directed toward management of the palatal abnormality
   4. Perioperative care of the neonate and infant with PRS (Cladis et al. 2014)
      1. The primary concern is upper airway obstruction with subsequent respiratory distress and feeding difficulty.
      2. The later may manifest as reflux and failure to thrive. PRS comprises a heterogeneous group of patients.
      3. Some may present with an isolated mandibular abnormality, while other patients with PRS have associated anomalies or syndromes.
      4. The patient with mild airway obstruction can be managed conservatively with nasopharyngeal airways, prone positioning, and mechanical feeders.
      5. Moderate or severe obstruction requires more invasive interventions such as gastrostomy tube placement, tongue-lip adhesion, mandibular distraction osteogenesis, and tracheostomy.
   5. Surgical intervention for upper airway obstruction (Bath and Bull 1997; Scott et al. 2012)
      1. Glossopexy/tongue-lip adhesion (Argamaso 1992) to bring tongue forward and attach it to an anterior structure to prevent the tongue from falling back into the airway
      2. Tracheotomy (Myer et al. 1998) needed only in cases where conservative treatments fail
      3. Mandibular distraction osteogenesis (surgical incision of the mandible followed by the application of traction to stimulate new bone growth): reduces cleft palate width and lengthens soft palate, influencing palatoplasty in patients with Pierre Robin sequence (Collares et al. 2016)
      4. Repair of cleft palate
   6. Treat middle ear infections
      1. Antibiotics
      2. Placement of tympanostomy tubes
   7. Speech therapy

References

Acke, F. R., Dhooge, I. J., Malfait, F., et al. (2012). Hearing impairment in Stickler syndrome: A systematic review. *Orphanet Journal of Rare Diseases, 7*, 1–10.

Argamaso, R. V. (1992). Glossopexy for upper airway obstruction in Robin sequence. *Cleft Palate Craniofacial Journal, 29*, 232–238.

Barr, R. M., Khan, S. A., Shah, M. N., et al. (2016). Cervical instability in Pierre Robin sequence. *Journal of Craniofacial Surgery*. [Epub ahead of print].

Bath, A. P., & Bull, P. D. (1997). Management of upper airway obstruction in Pierre Robin sequence. *Journal of Laryngology and Otology, 111*, 1155–1157.

Breugem, C. C., Evans, K. N., Poets, C. F., et al. (2016). Best practices for the diagnosis and evaluation of infants with Robin sequence: A clinical consensus

report. *JAMA Pediatrics*. doi:10.1001/jamapediatrics.2016.0796. [Epub ahead of print].
Buchanan, E. P., Xue, A. S., & Hollier, L. H., Jr. (2014). Craniofacial syndromes. *Plastic and Reconstructive Surgery, 134*, 128e–153e.
Bush, P., & Williams, A. (1983). Incidence of the Robin anomalad. *British Journal of Plastic Surgery, 36*, 434–437.
Carey, J., Fineman, R., & Ziter, F. (1982). The robin sequence as a consequence of malformation, dysplasia, and neuromuscular syndromes. *Journal of Pediatrics, 101*, 858–864.
Cladis, F., Kumar, A., Grunwaldt, L., et al. (2014). Pierre Robin sequence: A perioperative review. *Anesthesia and Analgesia, 119*, 400–412.
Cohen, M. M., Jr. (1976). The Robin anomalad – Its nonspecificity and associated syndromes. *Journal of Oral Surgery, 34*, 587–593.
Cohen, M. M., Jr. (1999). Robin sequences and complexes: Causal heterogeneity and pathogenetic/phenotypic variability. *American Journal of Medical Genetics, 84*, 311–315.
Collares, M. V. M., Duarte, D. W., Sobral, D. S., et al. (2016). Neonatal mandibular distraction osteogenesis reduces cleft palate width and lengthens soft palate, influencing palatoplasty in patients with Pierre Robin sequence. *Journal of Craniofacial Surgery, 27*, 1267–1272.
Da Costa, J. N., & Matias, J. (2014). Isolated Robin sequence in siblings: Review of current concepts. *Journal of Plastic, Reconstructive & Aesthetic Surgery, 67*, e259–e265.
DeHaan, K. L., Seton, C., Fitzgerald, D. A., et al. (2015). Polysomnography for the diagnosis of sleep disordered breathing in children under 2 years of age. *Pediatric Pulmonology, 50*, 1346–1353.
Evans, K. N., Sie, K. C., Hopper, R. A., et al. (2011). Robin sequence: From diagnosis to development of an effective management plan. *Pediatrics, 127*, 936–948.
Hanson, J. W., & Smith, D. W. (1975). U-shaped palatal defect in the Robin anomaly: Developmental and clinical relevance. *Journal of Pediatrics, 87*, 30.
Heaf, D., Jelms, P., Dinwiddie, R., et al. (1982). Nasopharyngeal airways in Pierre Robin syndrome. *Journal of Pediatrics, 100*, 698–703.
Holder-Espinasse, M., Abadie, V., Cormier-Daire, V., et al. (2001). Pierre Robin sequence: A series of 117 consecutive cases. *Journal of Pediatrics, 139*, 588–590.
Hsieh, Y.-Y., et al. (1999). The prenatal diagnosis of Pierre Robin sequence. *Prenatal Diagnosis, 19*, 567–569.
Jakobsen, L. P., Knudsen, M. A., Lespinasse, J., et al. (2006). Genetic basis of the Pierre robin sequence. *The Cleft Palate-Craniofacial Journal, 43*, 155–159.
Kadakia, S., Helman, S. N., Bradhey, A. K., et al. (2014). Treacher Collins syndrome: The genetics of a craniofacial disease. *International Journal of Pediatric Otorhinolaryngology, 78*, 893–898.
Marcus, C. L., Brooks, L. J., Draper, K. A., et al. (2012). American Academy of Pediatrics. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics, 130*, 576–584.
Myer, C. M., III, Reed, J. M., Cotton, R. T., et al. (1998). Airway management in Pierre Robin sequence. *Otolaryngology and Head and Neck Surgery, 118*, 630–635.
Pilu, G., Rombero, R., Reece, A., et al. (1986). The prenatal diagnosis of Robin anomalad. *American Journal of Obstetrics and Gynecology, 154*, 630–632.
Randall, P., Krogman, W. M., & Jahina, S. (1965). Pierre Robin and the syndrome that bears his name. *The Cleft Palate Journal, 2*, 237–244.
Robin, P. (1923). La chute de la base de la langue considérée comme une nouvelle cause de gene dans la respiration naso-pharyngienne. *Bulletin de l'Académie nationale de médecine (Paris), 89*, 37–41.
Rosa, R. F. M., Guimarães, V. B., Beltrao, L. A., et al. (2015). Nager syndrome and Pierre Robin sequence. *Pediatrics International, 57*, e69–e72.
Scott, A. R., Tibesar, R. J., & Sidman, J. D. (2012). Pierre Robin sequence: Evaluation, management, indications for surgery, and pitfalls. *Otolaryngology Clinics of North America, 45*, 695–710.
Sheffield, L. J., Reiss, J. A., Strohm, K., et al. (1987). A genetic follow-up study of 64 patients with the Pierre Robin complex. *American Journal of Medical Genetics, 28*, 25–36.
Shprintzen, R. J. (1988). Pierre Robin, micrognathia, and airway obstruction: The dependency of treatment on accurate diagnosis. *International Anesthesiology Clinics, 26*, 64–71.
Shprintzen, R. J. (1992). The implications of the diagnosis of Robin sequence. *Cleft Palate-Craniofacial Journal, 29*, 205–209.
Shprintzen, R. J. (2001). Robin sequence. In S. B. Cassidy & J. E. Allanson (Eds.), *Management of genetic syndromes* (pp. 323–336). New York: Wiley-Liss.
Sidhu, S. S., & Deshmukh, R. N. (1989). Pierre Robin syndrome: Autosomal dominant inheritance with pleiotropic effect. *Indian Journal of Pediatrics, 56*, 413–417.
Taylor, M. R. G. (2001). The Pierre Robin sequence: A concise review for the practicing pediatrician. *Pediatrics in Review, 22*, 125–130.
Tewfik, T. L., Trinh, N., & Teebi, A. S. (2015). Pierre robin syndrome. *eMedicine* from WebMD. Retrieved 6 Nov 2015. Available at: http://emedicine.medscape.com/article/844143-overview
Van den Elzen, A. P. M., Semmekrot, B. A., Bongers, E. M. H. F., et al. (2001). Diagnosis and treatment of the Pierre Robin sequence: Results of a retrospective clinical study and review of the literature. *European Journal of Pediatrics, 160*, 47–53.
Williams, A. J., Williams, M. A., Walker, C. A., et al. (1981). The Robin anomalad (Pierre Robin syndrome) – A follow-up study. *Archives of Disease in Childhood, 56*, 663–668.

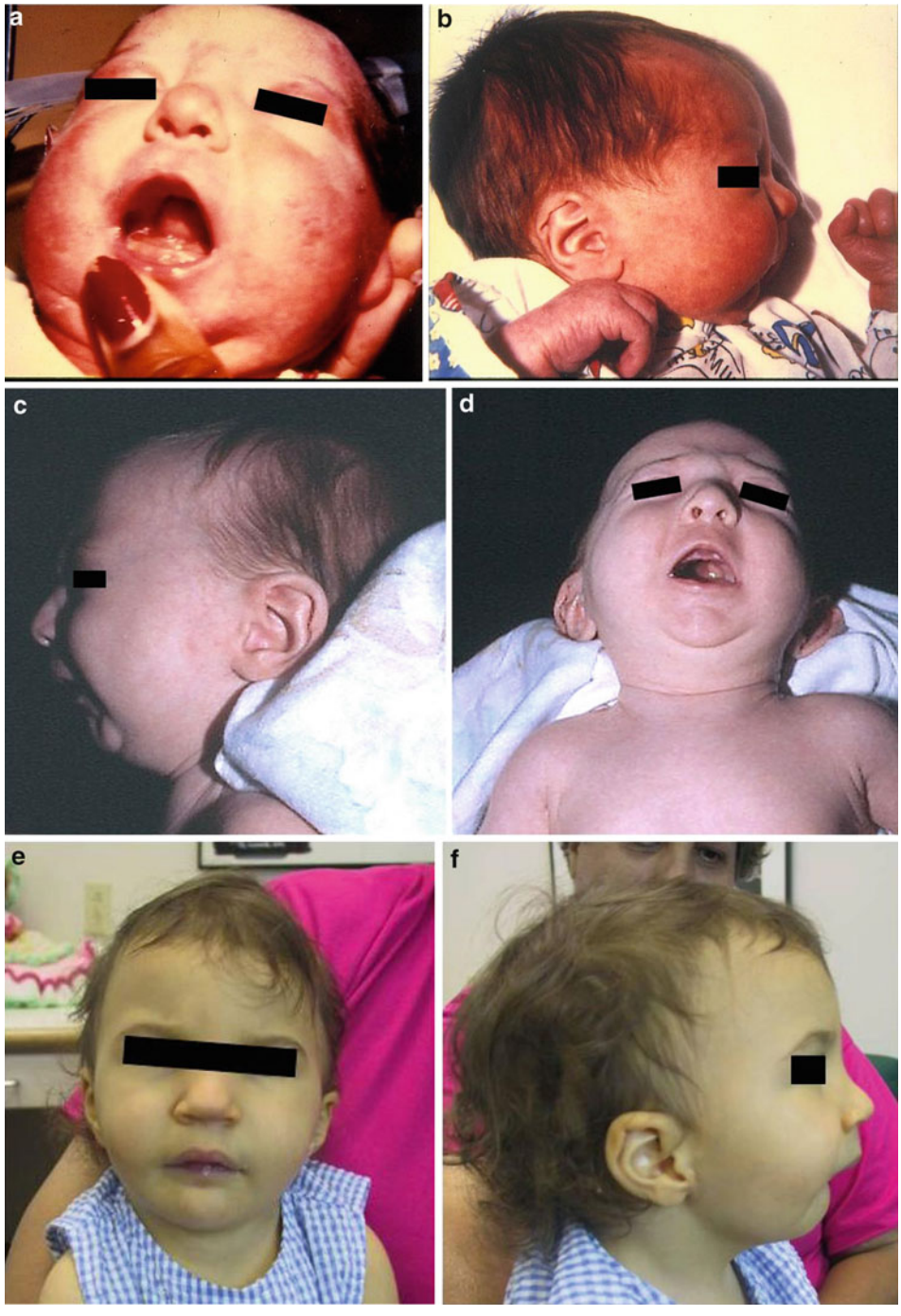

Fig. 1 (**a**–**f**) Three infants (**a**, **b**; **c**, **d**; **e**, **f**) with typical Pierre Robin sequence