Pierre Robin Sequence

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Synonyms of Pierre Robin Sequence

- glossoptosis, micrognathia, and cleft palate
- PRS
- Robin syndrome

General Discussion

Summary

Pierre Robin sequence (PRS) is characterized by a small lower jaw (micrognathia) and displacement of the tongue toward the back of the oral cavity (glossoptosis). Some infants also have an abnormal opening in the roof of the mouth (cleft palate). PRS is believed to be caused by multiple contributing factors, which lead to a series of physical changes within the oral cavity. The current belief is that the lower jaw does not grow enough, which leads to the tongue being displaced toward the back of the throat. Given the oral cavity's limited size, the tongue also gets pushed upward, where it interferes with the natural closure of the developing palate. These changes occur during pregnancy, leading to craniofacial abnormalities that are typically detected at birth. Additionally, the altered anatomy of the oral cavity makes breathing difficult, which can range in severity from mild disturbance to life-threatening respiratory distress. Since food must pass through the altered oral cavity to get into the gastrointestinal tract, feeding difficulties are also common. The features of PRS can be present as an isolated sequence or as part of a genetic syndrome. Individuals with isolated PRS most commonly have mutations near the *SOX9* gene.

Introduction

PRS is a condition with several clinical features: a small lower jaw (micrognathia), displacement of the tongue toward the back of the oral cavity (glossoptosis) and, often but not always, an opening in the roof of the mouth (cleft palate). PRS was named after Dr. Pierre Robin, a French dental surgeon who first observed its features during the early 20th century. While the precise cause is not fully clear, the current belief is that

multiple contributing factors lead to sequential physical changes within the oral cavity, which ultimately leads to airway obstruction. For this reason, breathing problems are common manifestations of PRS. Feeding problems are also common, since the oral cavity also serves as a conduit to the gastrointestinal tract.

Signs & Symptoms

PRS involves physical changes during development that lead to altered oral cavity anatomy. Since air and food both pass through the mouth and down the throat, breathing and feeding problems are common.

In PRS, the lower jaw (mandible) characteristically has an altered shape and position. Typically, it has a reduced length and is located toward the back (microretrognathia). In turn, these changes in the mandible can influence the tongue's positioning toward the back of the mouth (a 'retruded' tongue). Anatomic anomalies of PRS also frequently include a U-shaped cleft palate, which affects the dynamics of breathing and speech development.

Specifically, the displacement of the tongue toward the back (posterior) of the mouth predisposes it to fall toward the throat. This may obstruct the airway and cause difficulty breathing. This can vary in severity, ranging from mild disturbance to life-threatening respiratory distress. Airway obstruction can also occur during the night, in the case of a related condition called 'obstructive sleep apnea'. This is a sleep disorder characterized by breathing that temporarily stops and restarts because of periodic blockage of the airways.

Since food traveling toward the gastrointestinal tract also passes through the mouth and throat, feeding difficulties can also arise due to abnormal oral cavity anatomy. Depending on the severity, this can lead to issues like choking (aspiration) or gaining less weight gain than expected (which doctors refer to as 'failure to thrive'). There is also a higher prevalence of acid (gastroesophageal) reflux in children with PRS.

Other possible manifestations of PRS include cardiovascular and lung conditions, such as heart murmurs, high blood pressure in the arteries of the lungs (pulmonary hypertension), and narrowing of the opening between the lung artery and the right ventricle of the heart (pulmonary stenosis). Anomalies of the musculoskeletal system, including those in the arms, legs, feet, and vertebral column, are also common. Inflammation of the middle ear (otitis media) usually accompanied by repeat ear infections occurs in about 80% of patients, and eye (ocular) defects are noted in about 10% to 30% of patients. Teeth present at birth (natal teeth) are another frequent finding.

Causes

At present, the exact cause of PRS is unknown. The most widely held view is that multiple contributing factors lead to a sequence of physical changes within the oral cavity. These changes are thought to occur in a series of steps, rather than as isolated

events. Specifically, it is believed that failure of the lower jaw to fully develop early in gestation causes the tongue to be positioned toward the back and high up in the mouth cavity, which, in turn, prevents palate closure.

PRS as a condition can occur by itself ('isolated PRS') or as a feature in multiple anomaly disorders ('syndromic PRS'). When PRS occurs on its own, DNA near a gene called *SOX9* is the most commonly affected region. The *SOX9* gene allows for the production of the SOX9 protein, which plays a critical role in skeletal development. In affected individuals, there are often mutations in regions of DNA that positively modulate *SOX9*'s activity (enhancers). When these areas are damaged, the *SOX9* gene's activity is reduced, which leads to less normal SOX9 protein being produced. This is believed to play a role in the craniofacial abnormalities characteristically associated with PRS.

At present, most cases of isolated PRS are believed to arise sporadically, or through new (de novo) genetic changes, rather than being inherited from one generation to the next. In the rarer familial cases of isolated PRS, research has favored an autosomal dominant mode of inheritance. Syndromic PRS is inherited following the same genetic pattern as the condition that it is associated with, meaning that this may vary depending on the syndrome.

Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary to cause a particular disease. The abnormal gene can be inherited from either parent or can be the result of a mutated (changed) gene in the affected individual. The risk of passing the abnormal gene from an affected parent to an offspring is 50% for each pregnancy. The risk is the same for males and females.

Affected Populations

PRS affects males and females in equal numbers, with an estimated prevalence of about 1 in 8,500-14,000 individuals.

Related Disorders

Symptoms of the following disorders can be similar to, or may be associated with, PRS. Comparisons may be useful for a differential diagnosis.

Stickler syndrome is a rare connective tissue disorder that most often affects the eyes, ears, skeleton, and joints. Signs and symptoms may include: nearsightedness (myopia), a detached retina (separation of the retina of the eye from the layers of the eyeball that support it), hearing loss, a characteristic facial appearance with mid-facial flatness, and joint pain. Affected individuals may also have features of PRS, specifically an unusually small lower jaw (micrognathia), displacement of the tongue toward the back of the oral cavity (glossoptosis) and an abnormal opening in the roof of the mouth (cleft palate). (For more information on this disorder, choose "Stickler" as your search term in the Rare Disease Database.)

Chromosome 22q11.2 deletion syndrome (velocardiofacial syndrome) is a disorder

caused by a small piece of chromosome 22 missing. 22q11.2DS is associated with a range of problems including: congenital heart disease, palate abnormalities, immune system dysfunction including autoimmune disease, low calcium (hypocalcemia) and other endocrine abnormalities such as thyroid problems and growth hormone deficiency, gastrointestinal problems, feeding difficulties, kidney abnormalities, hearing loss, seizures, skeletal abnormalities, minor facial differences, and learning and behavioral differences. The symptoms of this condition are extremely variable, even among members of the same family. (For more information on this disorder, choose "chromosome 22q11.2 deletion" as your search term in the Rare Disease Database.)

Treacher Collins syndrome is a rare genetic disorder characterized by distinctive abnormalities of the head and face, notably severe micrognathia. Associated manifestations include malformation of the eyes, anomalies of the ear that may lead to hearing loss, and more. (For more information on this disorder, choose "Treacher Collins" as your search term in the Rare Disease Database.)

Other related syndromes and conditions include: chromosome 11, partial trisomy 11q; trisomy 18 syndrome; cerebro-costo-mandibular syndrome; Catel Manzke syndrome; campomelic dysplasia; Moebius syndrome; and CHARGE syndrome. NORD has individual reports on many of these disorders. (For more information, choose the specific disorder name as your search term in the Rare Disease Database.)

Diagnosis

PRS can be detected while the fetus is still in the womb. Trained medical personnel may visualize characteristic features of PRS using ultrasound imaging. If not diagnosed previously, craniofacial abnormalities are typically detected at birth on physical exam. Infants with severe airway obstruction may present with respiratory distress at birth, and may require medical intervention.

There is no one standard test that is routinely used to diagnose isolated PRS, though molecular genetic testing can be used to identify DNA changes involving the *SOX9* gene.

If syndromic PRS is suspected, consultation with a geneticist is highly recommended. This healthcare professional may carry out a laboratory workup in support of the suspected condition.

Standard Therapies

Treatment
Treatment of PRS is multifaceted and individualized, with surgery being performed only to solve the functional problems that a patient may have. Surgical treatments may be indicated for PRS patients with more severe clinical conditions, often those associated with airway impairment.

Infants with PRS should be observed closely for breathing difficulties. Placing the child on his or her stomach (prone position), rather than on his or her back, can help prevent

the tongue from falling back toward the throat. If this does not solve the problem of airway obstruction, small tube-like instruments such as a 'nasopharyngeal airway' may be inserted into the nose to keep the airways open. If airway obstruction is even more severe, a tube may be inserted in the infant's throat in hospital (intubation) or, rarely, a surgical opening may be made into the trachea through the neck (tracheostomy) to assist the infant in breathing.

To close the cleft palate, surgery is typically performed between 12 and 18 months of age. Doctors may postpone the corrective surgery, however, to allow the opening in the palate to close on its own as natural growth occurs.

Surgery to improve the appearance of the jaw is rarely necessary because the small lower jaw seen at birth most often grows to a more normal size by 18 months of age. To address feeding-related difficulties, a variety of specially adapted bottles and nipples may be used. If feeding problems are unresolved and severe, a feeding tube may be needed temporarily in order to assist with proper weight gain.

Symptomatic and supportive treatment may be provided using a multidisciplinary team approach, in order to best meet the needs of the affected individual. If speech is impaired, the child should participate in speech therapy or be monitored by a speech pathologist. Ear, nose, and throat doctors (otolaryngologists) and audiologists can provide follow-up on ear- and hearing-related issues. Surgically placed drainage tubes may be recommended if ear infections are recurrent. A combination of orthodontists, maxillofacial surgeons, and dentists may work together to monitor the oral cavity, for example by looking to avoid crowding of the teeth and to ensure proper tooth alignment. Ophthalmology may be consulted to monitor for ocular abnormalities. Genetic counseling may be of benefit for patients and their families.

Investigational Therapies

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government Web site.

For information about clinical trails being conducted at the National Institutes of Health (NIH) Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Tollfree: (800) 411-1222
TTY: (866) 411-1010
Email:

Some current clinical trials also are posted on the following page on the NORD website: https://rarediseases.org/for-patients-and-families/information-resources/info-clinical-trials-and-research-studies/

For information about clinical trials sponsored by private sources, contact: http://www.centerwatch.com/

For information about clinical trials conducted in Europe, contact: https://www.clinicaltrialsregister.eu/

NORD Member Organizations

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Email:
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Other Organizations

- Birth Defect Research for Children, Inc.
  976 Lake Baldwin Lane
  Orlando, FL 32814 USA
  Phone: (407) 895-0802
  Email:
  Website: http://www.birthdefects.org
- Cleft Lip and Palate Foundation of Smiles
  2044 Michael Ave SW
  Wyoming, MI 49509
  Phone: (616) 329-1335
  Email:
  Website: http://www.cleftsmile.org
- FACES: The National Craniofacial Association
  PO Box 11082
  Chattanooga, TN 37401
  Phone: (423) 266-1632
  Toll-free: (800) 332-2373
  Email:
  Website: http://www.faces-cranio.org
- Genetic and Rare Diseases (GARD) Information Center
  PO Box 8126
  Gaithersburg, MD 20898-8126
  Phone: (301) 251-4925
  Toll-free: (888) 205-2311
  Website: http://rarediseases.info.nih.gov/GARD/

- Let Them Hear Foundation
  1900 University Avenue, Suite 101
  East Palo Alto, CA 94303
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  Email:
  Website: http://www.letthemhear.org

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