Case Study—Primary Care

Pierre Robin Sequence: A “Stickler” Situation?

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KEY WORDS
Pierre-Robin sequence, Stickler syndrome, cleft palate, genetic syndromes

CHIEF COMPLAINT
A 6-month-old White girl who was born with Pierre Robin sequence (PRS) presents to the pediatric clinic for a scheduled health maintenance examination.

HISTORY OF PRESENT ILLNESS
The patient was born to a healthy gravida 2, para 2, 27-year-old woman. There was no intrauterine exposure to medications, alcohol, recreational drugs, or tobacco. The infant was delivered vaginally at 38 weeks' gestation in a local hospital. Her statistics at birth were as follows: weight, 3.58 kg (25th to 50th percentile); length, 51 cm (50th percentile); head circumference, 33.3 cm (10th to 25th percentile); and Apgar score, 8 and 9. Upon delivery, the patient was noted to have a U-shaped complete cleft palate and a small chin. She had some respiratory difficulties and was transferred to a children’s medical center for airway stabilization. Consultations with an ear, nose, and throat (ENT) specialist and plastic surgeon were conducted prior to her discharge from the hospital.

MEDICAL/SURGICAL HISTORY
At 1 month of age, the patient had progressive difficulty in sucking and swallowing. The parents consulted with a pediatric speech therapist and cleft palate specialist to ensure that proper feeding techniques were being used. Despite the use of special bottles and nipples, the patient continued to have difficulty sucking and swallowing formula, as demonstrated by her poor weight gain of 3.67 kg (25th percentile). The patient experienced bilateral otitis media at 2 months of age; a myringotomy was performed and pressure equalization (PE) tubes were inserted. She also exhibited sleep apnea and had difficulty maintaining a patent airway. A partial airway obstruction was confirmed from a sleep study performed at 2 months. Her weight gain was also slowing down, and it was noted at her 2-month examination that she only weighed 4 kg (10th percentile).

Because of her persistent airway obstruction, mandibular distraction osteogenesis was performed when the patient was 3 months old. Following this operation, her feeding problems continued. Her weight was 4.3 kg (5th to 10th percentile). A swallow study was done that showed laryngeal penetration with thin liquids that had the consistency of nectar, and a gastrostomy button (g-button) was inserted. At 4 months, her mother reported improved feedings, as evidenced by her increasing weight of 5.36 kg (10th to 25th percentile).

At 5 months of age, the patient had an initial visit with a pediatric geneticist. The diagnosis of PRS was...
officially confirmed as a result of this examination. Genetics testing was ordered to determine if PRS was a component of a genetic syndrome.

The patient has been seen by a pediatric nurse practitioner (PNP) every 2 weeks since hospital discharge. These visits served to assess weight gain and to provide support for her family. Her immunizations are current, and family members received their seasonal and H1N1 influenza vaccines this year. The patient receives a liquid multivitamin with iron through her g-button daily. A pediatric nutritionist manages her caloric intake and formula feedings.

FAMILY HISTORY
The patient lives at home with both parents and her 8-year-old half brother. Her parents report that they do not smoke or consume illicit drugs or alcoholic beverages. They have completed high school and some college courses and both report that they are in good health. Her brother is healthy and currently is seeing a pediatric health care provider for suspected attention deficit hyperactivity disorder. All extended maternal and paternal family members are reported to be in good health. There are no reported genetic syndromes on either side of the family (see Appendix for pedigree).

PERSONAL/SOCIAL HISTORY
The family is very involved in their local church, where they attend weekly worship services. The patient does not participate in church nursery activities because of the risk of contracting infection or illness. Her parents do not attend any PRS or cleft palate support groups. The patient’s father has recently changed jobs and has lost his private health insurance benefits for the family. The patient presently is enrolled in a state-funded insurance program.

REVIEW OF SYSTEMS
The review of systems reveals some subtle yet important information for the PNP. The mother reports that the patient’s eyes appear to focus well and have not crossed since she was 1 month of age. She has not taken the patient to an ophthalmologist and does not recall receiving a referral for an appointment with an eye doctor. The mother states, “Her vision seems normal.” In her oropharynx, the patient will not suck on a nipple and only chews on it. Small amounts of baby food are offered by spoon; however, she does not eat more than a teaspoonful. Although she meets with a speech and physical therapist on a weekly basis, the patient is slow to make progress. Closure of the cleft palate is planned when she is 12 months old. The mother reports that the patient has an occasional loose, productive cough. She is able to clear secretions “better” during the past few weeks and suctioning is not required. No respiratory distress has been noted since her jaw surgery. With regard to her growth and development, the mother verbalizes that the patient is “a little slower” than other children who are the same age. The patient “laughs and babbles like other babies” but is unable to roll from her back to her stomach. She does not rock on her hands and knees but “scoots” and rotates in circles when placed on her abdomen. The patient has an appointment with a pediatric neurologist next month.

PHYSICAL EXAMINATION
A well-groomed, 6-month-old White girl presents with her biologic mother for her 6-month examination. She weighs 6.22 kg (10th to 25th percentile), is 67 cm in length (90th percentile), and has a head circumference of 41 cm (25th percentile). The patient’s forehead is slightly prominent; her anterior fontanel measures 3 cm and is soft, flat, and pulsatile. Her hair is finely textured and evenly dispersed on her scalp. Her chin is pulled into a normal position, and the distraction apparatus is intact bilaterally. Her trachea is midline and her neck is supple without masses or lymphadenopathy. Her skin is pink and supple and free of rashes or areas of hypopigmentation or hyperpigmentation. Her eyes are deep set and her sclera, irides, and fundi are normal. No strabismus, ptosis, or epicanthal folds are noted.

Both of her ears are cupped. She has no ear protrusions or unusual ear structure or markings. The ear canals are pink without discharge or exorriations. Her PE tubes are intact and her tympanic membranes are translucent and pearly, with landmarks noted bilaterally. Her nose is small, patent, symmetric, and centrally positioned on her face. Her turbinates are pink without discharge or erythema. The philtrum, lips, and mouth are well formed. Her palate shows a large, rounded notch. The patient is able to move her jaw; no teeth are present, and her tongue rests on the floor of her mouth.

Heart sounds are normal, and no murmur is appreciated. All pulses are present, strong, and equal. The chest is symmetric with two areolae present and symmetrically aligned. Her lungs are clear to auscultation. The abdomen is soft with bowel sounds present in all quadrants, with no organomegaly appreciated. The g-button is intact without leakage, redness, or odor. Tanner I external female genitalia is observed. The anus is patent and an intact sphincter is noted. No redness, odor, or diaper rash are present.

The upper extremities appear to be in proportion. Palmar creases, fingernails, and joints are normal bilaterally. She is noted to have long fingers, confirmed by bilateral middle finger lengths, which are 3.7 cm (97th percentile). Her lower extremities are in proportion, and her feet, toes, toenails, and joints appear normal.
Her back is straight and intact, and no hair tufts or dimpling are noted. All cranial nerves are intact. Her reflexes are symmetric—1+ in the upper and lower limbs. Muscle tone, strength, and mass are within normal limits. The patient sits momentarily (<2 seconds unattended). She is able to lift her chest up well in the prone position. She reaches and grabs for objects and puts them into her mouth. She is unable to crawl when in the prone position. Vocal noises were made, but no specific sounds or words were elicited. No apprehension of strangers was demonstrated.

**CASE STUDY QUESTIONS**

1. What is the etiology of PRS?
2. What complications are associated with PRS?
3. What differential diagnosis should be considered for this patient?
4. What is your management plan for this patient at this time?

**CASE STUDY ANSWERS**

1. **What is the etiology of PRS?**

   PRS occurs in 1:800 live births, is more frequent in males, and has a greater incidence among twins. It can occur as an isolated event in which heredity is not a factor. Examples of isolated or non-syndromic causes of PRS are intrauterine positional malformation, amniotic bands, uterine fibroids, maternal alcohol use, and teratogenic exposures. PRS also can occur as a result of a mode of inheritance, occurring in association with other syndromes such as Stickler, DiGeorge (velocardiofacial), and Treacher-Collins syndromes (Evans, Rahbar, Rogers, Mulliken, & Volk, 2006).

   A sequence is a group of related anomalies that originate from a single initial anomaly that causes an alteration in surrounding tissues or structures. PRS is identified clinically by micrognathia (a small lower jaw) or retrognathia (lower jaw displaced to the back), glossoptosis (displacement of the tongue into the throat), and a U-shaped or rounded cleft palate.

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**DIAGNOSTIC TESTING**

The parents were notified via a telephone call from the genetics clinic that results of all laboratory tests were normal. Her initial chromosome study (a quick genetic screen) revealed no abnormalities on the 13, 18, 21, X, or Y chromosomes. The microassay showed 22 paired autosomes and one pair of sex chromosomes, XX. No gross chromosomal abnormality was detected. On the fluorescent in situ hybridization (FISH) test, two copies of 22q1.11q were present.

Approximately 50% of PRS cases are attributed to genetic heritability. The initial chromosome study reveals matching pairs of chromosomes 13, 18, 21, and X. There is no Y chromosome. The major trisomy disorders (trisomy 13, 18, and 21) and chromosomal aneuploidies (Turner [XO] and Kleinfelter [XXY]) have been associated with cleft palate and PRS (Descartes & Carroll, 2007). The microassay reveals 22 matching pairs of autosomes and one pair of female sex chromosomes. A microassay is not a comprehensive genetic test because it is unable to detect small rearrangements, microdeletions, or low levels of mosaicism (Lewis, 2008). The FISH test was ordered to determine if she carried a deletion in the 22q1.11q chromosome. Defects on this chromosome can produce alterations in immune function and can be fatal without proper identification and treatment (Jones, 2006; Lewis, 2008). The FISH test determined that two complete copies of 22q1.11q were present. However, PRS occurs in many other malformation syndromes unable to be detected by these three tests. If the health care provider suspects other hereditable syndromes, additional FISH testing must be ordered (Jones, 2006).
2. What complications are associated with PRS?

Respiratory distress is the greatest concern with patients who have PRS. Primary management is determined by the severity of the respiratory manifestations. Some patients can be managed with non-surgical interventions, such as prone positioning and use of a nasopharyngeal tube. In severe cases, surgical intervention is necessary, and some patients also may require a tracheotomy (Cole et al., 2008). This patient exhibited progressive respiratory distress episodes that impaired her ability to breathe and eat. Failure to correct recurrent episodes of hypoxia could result in permanent cognitive deficits (Drescher et al., 2008). Her situation was further compounded by her cleft palate. Cleft palate accompanies PRS in approximately 50% of reported cases (Jones, 2006). Mandibular distraction osteogenesis is a surgical procedure that allows the jaw to lengthen and removes the airway obstruction by the tongue by allowing greater room on the floor of the mouth for the tongue to rest. This surgical procedure is very effective, and once the bones have begun to fuse, the metal appliances are removed (Evans et al., 2006).

Many infants with PRS experience weight loss, and a high rate of failure to thrive is reported (Evans et al., 2006). After her jaw surgery, this patient was unable to suck on specialized bottle nipples, so the g-button provided an alternate route for nutritional supplementation. Collaboration with a nutritionist and a cleft palate nurse educator can provide parents with proper instruction and support, which enables these infants to steadily gain weight. At this visit, her growth parameters were proportionate. Besides complicating feeding, a cleft palate can cause an increase in ear infections and varying degrees of hearing loss. Insertion of PE tubes prevents the recurrence of otitis media and scar tissue on the tympanic membranes and optimizes her hearing ability (Tinanoff, 2007).

3. What differential diagnosis should be considered for this patient?

Stickler syndrome (hereditary arthropthalmopathy, OMIM 184840) should be considered in any infant presenting with PRS. Stickler syndrome is the most common genetic syndrome that accompanies PRS. Although Stickler syndrome is rare, affecting 1:7500 newborns, PRS is present in approximately 30% of affected persons (Jones, 2006; Lee & Hayward, 2008). It is a collagen disorder that affects the ocular, craniofacial, cardiac, and musculoskeletal systems. It is autosomal dominant with incomplete penetration, making the systemic features of Stickler syndrome highly variable, and making affected and unaffected family members impossible to differentiate. In her pedigree, the patient has family members with myopia and cataracts. In persons with Stickler syndrome, myopia is present 90% of the time, and non-traumatic retinal detachment usually occurs before the age of 10 years. In addition, 70% of affected persons experience hearing loss and 46% have a mitral valve prolapse. Physical features include flat facies, arachnodactyly, and/or spondyloepiphyseal dysplasia. This patient had long middle finger and hand lengths. Severe joint pain often emerges during adolescence, mimicking juvenile rheumatoid arthritis (Lee & Hayward, 2008; Lewis, 2008).

4. What is your management plan for this patient at this time?

Because this child has not been evaluated by an ophthalmologist, the PNP should refer the patient to a pediatric ophthalmologist. According to Edwards (2008), primary health care providers do not routinely associate PRS with Stickler syndrome. The ocular manifestations in patients with Stickler syndrome are highly penetrant, and an eye examination is essential in making the diagnosis. Patients with Stickler syndrome have a distinctive vitreous appearance that makes the eye examination an important component of diagnosis and directs genetic testing for a CO2A1 mutation.

Abnormal ocular findings warrant further genetic testing. Appropriate genetic testing should be conducted for any infant who has PRS, cleft palate, and an abnormal ophthalmologic examination. There should be a high suspicion of Stickler syndrome when patients present with myopia and ocular lesions. The PNP should collaborate with the geneticist, and an additional FISH COL2A1 test (located on the 12q13.11-13.2 chromosome) should be ordered. If the ophthalmologic examination reveals myopia or early retinal detachment, the provider should make every effort to have this test ordered. Identifying the diagnosis of Stickler syndrome is important for the preservation of vision, supportive care for musculoskeletal deformities, recognition and treatment of hearing loss, and the provision of genetic counseling for families (Jones, 2006; Lee & Hayward, 2008; Shur & Abuelo, 2009).

Family planning and genetic counseling about the risks for recurrence of PRS and cleft palate should be discussed after the ophthalmologic examination. Based on the patient's presentation, there should be a high suspicion of Stickler syndrome when patients present with myopia and ocular lesions.
on the current findings, there is a 3% to 5% risk that PRS and cleft palate will recur in their future offspring. If this patient is discovered to have Stickler syndrome, there is a 50% chance that future offspring will inherit this condition (Lee & Hayward, 2008; Lewis, 2008).

This patient needs continual work to improve her sucking and chewing abilities. Her oral functioning will need to be re-evaluated by collaboration between the speech therapist, the oral surgeon, and the ear, nose, and throat specialist. In some instances, patients with PRS have decreased pharyngeal motor organization and increased dysphagia, requiring that some under- go electromyography to detect muscle dysfunction (Baudon et al., 2009). At this point it is premature to order an electromyography, so watchful waiting will determine if it will be needed in the future. In addition to the problems with her oral musculature, careful observation of her teeth eruption is important. Cleft palate can cause teeth eruption to be delayed and teeth to be malpositioned or absent. Collaboration with a pediatric dentist and orthodontist will be required (Tinanoff, 2007).

The patient also will need to be monitored for her speech development during the next few years. Ruiter, Korstein-Meijer, and Goorhuis-Brouwer (2009) note that children with cleft palate disorders have greater communication difficulties than do children with normally formed palates. They posit that language production and comprehension, hypernasality, and articulation peak during the toddler years. Patients with PRS and craniofacial deformities are at a greater risk for cognitive, behavioral, and emotional difficulties.

Parents of a chronically ill child can feel isolated, and the encouragement provided by local and on-line support groups must be underscored. The role of the PNP includes identifying the family’s needs and linking them with significant supportive resources (Drescher et al., 2008). The patient with PRS and cleft palate can present complicated management challenges for the PNP. Teamwork is necessary when treating pediatric patients with multifaceted issues, such as PRS and cleft palate. The inter-relatedness of hearing and speech requires coordination of care among multiple specialty groups. Communication between the PNP, geneticist, ENT specialist, oral surgeon, plastic surgeon, gastroenterologist, neurologist, audiologist, dentist, orthodontist, and physical and occupational therapist can be cumbersome and time consuming. The PNP, when functioning in the role of primary care provider, must help to coordinate multidisciplinary care for pediatric patients with complex conditions for optimal patient outcomes.

REFERENCES


