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Apert Syndrome

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Abstract

Apert Syndrome is a rare genetic disorder that presents with craniosynostosis, syndactyly and midface retrusion with dysostosis as well as many other anomalies. Apert Syndrome is an autosomal dominant syndrome that presents equally in males and females and has an occurrence rate of 1 in every 65,000. The incidence of this syndrome increases with the paternal age and is thought to be de novo in recurrence. Apert syndrome is a mutation on the FGFR 2 gene located on chromosome 10q25-26. Infants with Apert Syndrome will need a multidisciplinary approach as well as genetic counseling. This paper will clearly define the clinical presentation of an infant with Apert Syndrome as well as the surgical and medical management for this infant.

Introduction

Apert Syndrome, also known as acrocephalosyndactyly type 1, is a rare genetic disorder that presents in 1 out of every 65,000 births [1]. These infants present with craniosynostosis, midfacial dysostosis, and syndactyly and usually have multiple other anomalies that are associated with it. Apert Syndrome is an autosomal dominant syndrome that presents equally in males and females and a passed down through a de novo mutation.

Definition of the Disease, Incidence

Apert Syndrome was first described by a French physician, Eugene Apert. In 1906, he noticed that there were people who presented with similar facial and extremity characteristics. Even though Eugene only physically examined one patient himself in his clinic, he observed an addition nine people with similar characteristics. Eugene Apert described these Apert Syndrome characteristics as:

> I suggest the name, acrocephalosyndactyly to designate a type of teratology compatible with life and strongly characterized by the coexistence of the two following particularities: First, a high skull flattened in the back and sometimes at the sides, bulging on the opposite side to an exaggerated facet in the superior frontal region; second, syndactyly of the four extremities [2].

Today Apert Syndrome is defined as a "malformation syndrome characterized by a high short skull, underdevelopment of the midface, soft tissue and bony (mitten glove) fusion of fingers and toes, fusion of the neck vertebrae, and varying degrees of developmental delay" [3]. Apert Syndrome is categorized as a rare genetic disorder and occurs in 1 in every 65,000 infants born.

Disease Etiology and Pathogenesis

Apert syndrome is a mutation on the FGFR 2 gene located on chromosome 10q25-26. To understand how FGFR 2 affects people with Apert Syndrome, it is important to understand the foundation of FGFR 2 and the normal function of this particular gene. FGFR 2 stands for Fibroblast Growth Factor Receptor 2 Protein, which helps to transduce various ligands from the extracellular space to the intracellular space. These ligands help to create proliferation, differentiation, and apoptosis. These ligands provide specific instructions on how osteoblasts should form and the speed at which they should form.

In Apert Syndrome, there is a mutation on the FGFR 2 gene that suppresses differentiation and apoptosis of the osteoblasts [4]. Since apoptosis is suppressed, the FGFR 2 Protein become dysregulated and excessive which results in early ossification. This early ossification results in craniosynostosis, syndactyly, spinal fusions and multiple other dysostosis. These dysostoses then present with multiple dysmorphic features. These features and malformations lead to a cascading sequence of secondary effects [5].

Phenotype and Presentation

Clinical presentation

Craniosynostosis: One of the challenges of Apert

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Syndrome is that craniosynostosis affects multiple sutures, making surgical repair challenging. Depending on the degree and location of the ossification, facial presentation will vary. The types of suture involvement vary within Apert Syndrome. All infants will have fused coronal sutures while there is a high coinciding chance that the sagittal and lambdoid suture will be involved as well. Even though not all the sutures are not 100% affected, like the coronal suture, they still have high involvement. The sagittal suture is fused 85% of the time and the lambdoid suture is fused 81% of the time [6].

When all the sutures are affected, the infant will present with what is referred to as cloverleaf skull. Cloverleaf skull is defined as "a birth defect in which some or all of the usually separate bones of the skull have grown together resulting in a 3-lobed skull with associated deformities of the features and skeleton" [7]. This creates a sequence of structural defects that affect the treatment and management of infants with Apert Syndrome.

Midface retrusion dysostosis: Midface retrusion is an underdevelopment of the maxilla bones and has a greater impact on the vertical shape of the face. This underdevelopment leads to shallow orbits, down slanting palpebral fissures, a shorter maxillary bone, palatal and dental abnormalities, hearing impairment or loss of hearing, multilevel airway obstruction and neurological impairments. Each of these anomalies will be discussed in detail below.

Ocular abnormalities: Apert Syndrome infants will primarily present with proptosis and exophthalmos due to the shallow ocular orbits. Infants will also have down slanting palpebral fissure that will not allow the eyelid to completely cover the eye which places the infant at risk for corneal scarring. Other vision issues associated with Apert Syndrome are strabismus and anisometropia which can lead to amblyopia [6].

Syndactyly: Syndactyly occurs in all neonates with Apert Syndrome. This congential anomaly develops when the finger buds fail to differentiate during the fifth week of gestation and fuse together [8]. The types are syndactyly are classified as type I, type II and type III. Type I syndactyly is also referred to as the spade hand because fingers two through four are fused together in the shape of a spade. Type II, mitten or spoon, presents with a concave palm due to the fusion of the second to the fifth finger with webbing between the thumb and first finger. The final type of syndactyly is type III or the rosebud presentation. The rosebud is fusion of all the fingers in the hand with a single fingernail. Each of these types will present their own surgical challenges when repair is needed [9].

Spinal issues: Due to the ossification in infants born with Apert Syndrome, 68% of these infants will present with spinal fusion from C5-C6. Studies have show that there is a 50% occurrence rate of single fusions and a 50% chance of multiple fusions [6]. According to Thompson, spinal fusion is presenting as a progressive fusion rather that a congenital fusion.

Neurodevelopment: Infants with Apert Syndrome are shown to have normal intelligence or mild deficits. There are two main factors that will decrease an infant with Apert Syndrome intelligence level. The first factor is if the first craniotomy is performed after the age of one year old. The increase in the ICP may cause some neurological damage which will decrease the IQ of the infant. The second factor is the presence of any structural malformations of the brain. These abnormalities can be an abnormal corpus callosum or abnormalities of the septum pellucidum. It has also been reported that infants who received surgical intervention, medical treatment and early developmental therapy will have a better prognosis for their neurodevelopment.

Respiratory issues: Respiratory issues are a huge concern in infants that have Apert Syndrome. Due to the midface retrusion and dysostosis, infants are at risk for having a cleft palate, choanal atresia and narrowing of the nasal turbinates.

The initial presentation of choanal atresia in infants is that they will present with acrocyanosis while sleeping or eating and the acrocyanosis will disappear when the infant begins to cry. Infants with choanal atresia may present with unilateral or bilateral obstruction that results in respiratory distress of an infant. Respiratory distress is caused because infants are nose breathers. If the choanal atresia is unilateral, infants maybe able to breath sufficiently to not require surgical intervention. Yet, if bilateral choanal atresia is present, the infant will require an oral airway and immediate surgical intervention.

Another respiratory complication common in infants with Apert Syndrome is sleep apnea. Since the midface retrusion and dysostosis cause an abnormal shape of the face, infants may have nasal stenosis, a deviated septum, narrowed nasopharynx, cleft palate, palate swelling and/or a tracheal cartilage sleeve [10]. The infant maybe treated with continuous positive airway pressure until reconstructive surgery is performed.

Management

When an infant with Apert Syndrome is born, the physical characteristic will give a clear diagnosis of the syndrome. The first step to take is to talk to the family about Apert Syndrome and then get a definite confirmation with genetic tests. After those initial steps have been taken, a magnetic resonance imaging (MRI) or computed tomography (CT) scan is preformed on the infant to evaluate the degree in which the craniosynostosis is affecting the brain and the intercranial pressure (ICP). The MRI and CT will show the fused areas of the skull, any compressed nerves, and show any other sequential malformations that may have developed. When all the appropriate images have been obtained, the next step in management is to involve neurosurgery and reconstructive surgery. If the infant is presenting with Cloverleaf shape of the skull, neurosurgery will evaluate the ICP and place a shunt if needed. If the shunt alone is not sufficient, a craniotomy with shunt placement will be preformed. Infants who have a craniotomy with shunt placement will need to have further follow-up surgeries after three months of age.

Due to the shape of the head, many infants will require more than one cranial vault expansion. To prevent multiple

surgeries, a new procedure is being performed on infants with Apert Syndrome. This procedure is called a posterior vault distraction osteogenesis [11]. This type of procedure is when the coronal sutures are cut, and a distraction device is placed. The distracters are turned on and slowly expand to lengthen and enlarge the sutures to allow for optimal head expansion. Expansions of the sutures are done slowly to allow for the normal osteogenesis of the bone to regrow. This procedure is helping to create a more circular head shape rather that the traditional elongated shape and allows for ICP to gradually grow as the skull grows. By performing a PVDO, studies are showing a decrease in the amount of damage to ancillary bones and organs by decreases the amount of surgeries the infant will endure through their lifetime.

Another surgical intervention infant will need is facial reconstructive surgery. Around four years of age, the infant will need to have their cheeks and jaws extended to a normal position. The current modality for this surgery is called the LeFort III operation. The LeFort III reconstructive method starts by creating a 3D model of the face as well as a landmark-based morphometrics. From there, surgeons surgically remove part of the nasal bone and then extend the maxilla bones. By performing the LeFort III surgery, reconstructive surgeons are able to create a midline facial appearance. The LeFort III procedure will also increase the ability for the child to breath through their nose and help to decrease the residual effects of midface dysostosis.

Another line of management is to assess and monitor the airway of in Apert. Infants with Apert Syndrome have an increased risk of having upper airway deformities because of their midface retrusion and dysostosis. The primary upper airway obstruction is choanal atresia. Choanal atresia will cause respiratory distress in the infant and will need surgical intervention if it is bilateral. The preferred surgical intervention for treatment is called the transnasal endoscopic approach. The surgery is performed by inserting a drill to posterior to the nasal cavities, drilling holes and then placing nasal dilators or stents. These dilators or stents will remain in place of a couple of weeks and will be removed in the hospital if the infant is still a patient. In severe cases, an endotracheal tube will be inserted to ensure the passage stays open until the area is healed [12].

Another important disciplinary field for Apert syndrome is corrective and reconstruction surgery. According to Raposo-Amaral, hospital algorithms are changing to fit the whole needs of the infant rather than just focusing on each individual anomaly. Raposo-Amaral, is presenting the importance of reconstructive surgery of the hand as a primary focus that the infant is born without Cloverleaf presentation. Since infants learn at an early age how to grab items, hand surgery around four months of age will give the infant the ability to develop their gross and fine motor skills. By creating the ability to grasp items, family members will be able to promote independence and improve the quality of life for infants and their families. The modality for had surgery is the Upton hand type model. The Upton hand model focuses on how to preform limb digit separation while maintaining the nerves. The main goal of the Upton hand type surgery is to focus on creating five fingers separation by the end of surgical intervention. Surgical intervention is preferred to be performed by four months of life to prevent further fusion from happening. The three types of Upton hands are evaluated to create to the best outcome with the least number of surgeries. His surgical technique has shown to be the most effective and beneficial way to seperate digits.

Another management disciple that need to become involved in the management of Apert Syndrome is Early Intervention. An early intervention program is going to provide the infant and the family with skills to help the infant develop gross and fine motor skill, improve communication, help with feeding issue and encourage activities of daily living. A speech therapist will be important to help the infant with feeding issues as well as speech impairments. Infants with Apert Syndrome tend to have dental abnormalities, cleft palate and narrowing of the nasal turbinates. The speech therapist will help to assist the infant with correct tongue placement and proper cheek support to facilitate feeding and language development. A physical therapist is going to help with muscle tone, gait and balance. Infants with Apert syndrome have larger heads that require stronger neck muscles and upper body support. These infants also tend to have limb deformities and spinal fusions. Physical therapist will help to develop gross motor and maintain normal function. Physical therapist will also help to prevent further damages from happening and hopefully decrease the number of surgeries that the infant will need, except for cranial surgeries. Physical therapy will also help with stretches and movements that will help decrease pain in the body. Occupational therapists are going to help the infant with fine motor skills as well as how to function with any learning disabilities the infant might have. Occupational therapist help infants and children cope with their disability and give them the tools need to help cope. Occupational therapist will also teach and provide infants with assistive devices which will help the infant maintain mobility and stability.

Recurrence Risk and Genetic Counseling

Apert Syndrome is an autosomal dominate trait that is linked with the increase in the age of the father. It is reported that 95% of reported cases of Apert syndrome are de novo in form. This means that there is no know family history of Apert Syndrome and that it has occurred randomly. Due to Apert Syndrome being an autosomal dominate trait, there is a 50% chance that the parents will have another infant with Apert Syndrome [13].

It is important to provide genetic counseling to the family of an infant who has been diagnosed with Apert Syndrome. It will be recommended that the parents also have genetic testing done to see if they are carriers or if it is a de novo mutation. Genetic testing will provide them with the occurrence of another infant being born with Apert Syndrome but will also help to educate the family on future family planning if they consider having more children. Family planning will help to provide prenatal testing, reproductive option and potential risk to the future offspring.

Implications for Advanced Practice Nurse

The advanced practice nurse (APN) will need to have the knowledge on how to care for the dysmorphic infant. The APN will need to perform a thorough physical assess of the infant and treat according to the findings. Since infants with Apert Syndrome commonly present with respiratory distress, the APN will need to assess the best modality of respiratory treatment. The respiratory treatment will need to be followed with X-rays and blood gases if the infant is intubated. Respiratory support will then be titrated according to the blood gases.

Another implication that the APN is going to need to be able to treat are feeding issues. With the midface retrusion and the dysostosis, the infant will present with multiple feeding challenges. The APN is going to need to assess the infant's ability to orally feed and then will need to create a plan of care to manage hydration and nutritional status. This can be obtained through central line placement and eventually placement of a gastrostomy tube (G-Tube) if the infant will not be able to orally feed. The central line access will help provide access for medications and sedation during procedures and the G-tube will provide nutrition to help the infant grow and gain adequate weight.

The APN will need to take a collaboration approach to the care of the infant with Apert Syndrome. Referrals to physical therapy, occupation therapy and speech therapy. It will be important to have those therapies help the family perform safe infant care and help provide the infant with developmentally appropriate care. Since there will be a need for surgical intervention, the APN will need to consult the appropriate specialties. The APN and the specialties will develop a plan of care and treat the infant according to the care plan. The APN will also monitor the daily labs, vital signs and assessments and will adjust the plan of care accordingly. It is important for the APN to educate the family daily and help to give them support resources.

Conclusion

Infants with Apert Syndrome will require a clear and concise diagnosis to ensure they receive the correct medical and surgical intervention. It is important not to delay treatment of infants who present with Apert Syndrome to provide them with the best outcome. By knowing the clinical presentation as well as the management of Apert Syndrome, the APN will be able to correctly collaborate and treat the infant. The APN will know the importance for the multidisciplinary teamwork to provide the best possible outcome for the infant. With correct medical and surgical management, infants with Apert Syndrome have a chance of living a normal life.

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