International Journal of Advanced Science and Research
ISSN: 2455-4227; Impact Factor: RJIF 5.12
Received: 03-06-2019; Accepted: 05-07-2019
www.allsciencejournal.com
Volume 4; Issue 5; September 2019; Page No. 08-10

Pfeiffer syndrome: A forgotten disorder

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Abstract
Pfeiffer syndrome is a rare autosomal dominantly inherited disorder that associates craniosynostosis, broad and deviated thumbs and big toes, and partial syndactyly on hands and feet. Hydrocephaly may be found occasionally, along with severe ocular proptosis, ankylosed elbows, abnormal viscera, and slow development. Based on the severity of the phenotype, Pfeiffer syndrome is divided into three clinical subtypes. Type 1 "classic" Pfeiffer syndrome involves individuals with mild manifestations including brachycephaly, midface hypoplasia and finger and toe abnormalities; it is associated with normal intelligence and generally good outcome. Type 2 consists of cloverleaf skull, extreme proptosis, finger and toe abnormalities, elbow ankylosis or synostosis, developmental delay and neurological complications. Type 3 is similar to type 2 but without a cloverleaf skull. Clinical overlap between the three types may occur. Pfeiffer syndrome affects about 1 in 100,000 individuals. The disorder can be caused by mutations in the fibroblast growth factor receptor genes *FGFR-1* or *FGFR-2*. Pfeiffer syndrome can be diagnosed prenatally by sonography showing craniosynostosis, hypertelorism with proptosis, and broad thumb, or molecularly if it concerns a recurrence and the causative mutation was found. Molecular genetic testing is important to confirm the diagnosis. Management includes multiple-staged surgery of craniosynostosis. Midfacial surgery is performed to reduce the exophthalmos and the midfacial hypoplasia.

Keywords: craniosynostosis, syndactyly, brachycephaly, hypertelorism, proptosis

Introduction

Definition of Pfeiffer syndrome

Pfeiffer syndrome is a birth defect that causes problems with bones in a baby's skull, face, fingers, and toes. This syndrome mainly causes the sutures (joints) between skull bones to grow together too early, which prevents the head and face from growing normally and affects their shape.

Pfeiffer syndrome is a genetic disorder in which some seams of the skull fuse too early in prenatal development. It is a form of syndromic craniosynostosis that is generally characterized by a high forehead, bulging and wide-set eyes, an underdeveloped upper jaw and beaked nose, as well as abnormalities of the hands and feet.

Types of Pediatric Pfeiffer Syndrome

- Type I: Mildest and most common
- Type II: Most severe with neurological problems and a cloverleaf deformity caused by more skull bone fusion
- Type III: Similar to type II without the cloverleaf deformity

Type I

Patients with type I Pfeiffer syndrome usually have normal intelligence. Typically, craniosynostosis of both of the coronal sutures is present causing similar head shape to Apert syndrome. The skull is vertically tall and wide with the appearance of towering or leaning forward (turricephalic). The skull is very flat in the back and is short from front to back.

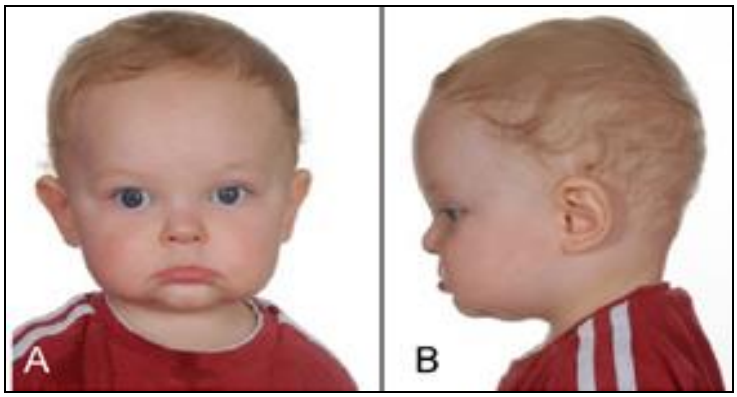

Fig 1

Type II

Patients with types II and III tend to have more severe medical problems and are more likely to have learning delays. Type II patients have a unique "cloverleaf" skull shape.

Fig 2

Type III

Type III patients generally have the most severe problems, but do not have a cloverleaf skull shape.

In general, all of these patients have eyes that look larger than normal. This is caused by a normal-sized eye sitting in a very shallow eye socket (orbit). The orbits are shallow because both the forehead and middle portion of the face are not able to grow forward like they should. Sometimes this makes it difficult for the eyelids to close fully, and patients can have problems with dry eyes. If this problem is severe, a surgery can help the eyelids close to protect vision. The orbits are also rotated outward and farther apart from one another, giving an abnormal downward tilt and wide spacing to the eyes.

The middle part of the face is vertically short and flat, coming from an undeveloped upper jaw. The palate is also highly arched. Often, the middle part of the face is placed so far back that these patients may not be able to breathe safely. These patients frequently need a tracheostomy to help them breathe safely. This problem is most common with type II and III patients; The upper and lower teeth are usually not lined up, which needs corrective surgery when the child is fully grown.

The thumbs and big toes of these patients are very large. This is a unique feature of Pfeiffer syndrome and can help diagnosis before genetic testing is complete. Occasionally, these patients will have a webbing of fingers (syndactyly).

Fig 3

Causes of Pfeiffer Syndrome

Pfeiffer syndrome is most commonly caused by mutations in the *FGFR2* gene. Mutations in the *FGFR1* gene cause a small percentage of cases of type 1 Pfeiffer syndrome. Mutations in this gene have not been associated with type 2 or 3.

The *FGFR1* and *FGFR2* genes provide instructions for making proteins known as fibroblast growth factor receptors 1 and 2, respectively. Among their multiple functions, these proteins signal immature cells to become bone cells during embryonic development. A mutation in either the *FGFR1* or *FGFR2* gene alters the function of the respective protein, causing prolonged signaling, which can promote the premature fusion of skull bones and affect the development of bones in the hands and feet.

Inheritance Pattern

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

Symptoms of Pfeiffer Syndrome

Pfeiffer syndrome is a complex genetic disorder that affects your child's head, face, hands and feet. Clinical features vary for different children and range from mild to severe. Pfeiffer syndrome may include:

- **Craniosynostosis**: Premature (early) closure of growth plates of the skull that changes the shape of the head and can put increased pressure on the brain. This makes skulls appear "too tall" and overly flat from the middle part of their faces upward.
- **Midfacial hypoplasia**: Decreased growth of the middle of the face, causing a sunken facial appearance. This can also cause potential airway obstruction, sleep apnea and a concave facial profile.
- **Proptosis**: Protruding, unprotected eyes
- **Brachydactyly**: Unusually short fingers and toes
- **Syndactyly**: Webbing or fusion between the fingers or toes

Other features of the condition may include

- Crowded teeth
- Cleft palate
- Some hearing loss, due to a defect in the middle ear
- Fused (joined) spinal bones
- Wide thumbs and big toes that bend away from the other digits

Pfeiffer Syndrome Diagnosis

Pfeiffer syndrome can be detected very early because of symptoms in the skull, thumbs, and big toes. Because skull deformities appear in several similar syndromes, other testing methods to make an accurate diagnosis.

The following tools to help diagnose Pfeiffer syndrome:

- X-rays to check for fused (missing) sutures on the top or sides of the head, or ridges along these sutures
- Diagnostic imaging, especially CT scans, also to check for fused sutures or ridges along sutures
- Genetic tests to rule out other syndromes for an accurate diagnosis and treatment

Treatments for Pfeiffer Syndrome

Treatment goals focus on -

- Correcting the skull and midface abnormalities and
- Treating obstructive sleep apnea.
- **Skull surgery**: Although the timing and sequence of surgeries may vary from child to child, most children

with Pfeiffer syndrome will need 2-4 skull operations over a lifetime. The earliest skull surgery is frequently done in the first 18 months of life.

- **Midface surgery**: The most common surgery for moving the bones of the midface forward in Pfeiffer syndrome is called a LeFort III operation. This surgery is typically not done before your child is 6-8 years of age. The primary indications for performing a LeFort III operation include severe obstructive sleep apnea which cannot be improved without surgery or significant patient concerns about appearance.
- **Obstructive sleep apnea**: Children with Pfeiffer syndrome frequently have obstructive sleep apnea due to the underdevelopment of the midface. As a result, your child should be monitored for sleep apnea by your craniofacial team. In mild cases of sleep apnea, medications may be sufficient to improve breathing. If more significant obstruction occurs, tonsillectomy or continuous positive airway pressure (CPAP) masks may help alleviate symptoms. Sometimes, a tracheostomy may be required in infants with Pfeiffer in order to ensure adequate breathing. Midface surgery, such as a LeFort III operation, may be needed as your child gets older in order to fully treat obstructive sleep apnea or allow for eventual removal of a tracheostomy placed in infancy. Ultimately, the goal in all of these interventions is to ensure a good airway so that your child can get enough oxygen to help her develop to her fullest potential.
    - Surgery to correct problems with the fingers or toes
    - Speech therapy to help with speech and language development.

Other name for this condition

- acrocephalosyndactyly, type V
- ACS V
- ACS5
- craniofacial-skeletal-dermatologic dysplasia
- Noack syndrome

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