PFEIFFER SYNDROME

Otherwise known as?

Pfeiffer syndrome is also known by the following names:

1. Craniofacial Dysostosis Type II
2. Craniofacial Syndrome Type II
3. Pfeiffer Syndrome with Syndactyly
4. Craniosynostosis with Syndactyly

These terms refer to the same genetic condition characterized by premature fusion of skull bones (craniosynostosis), leading to a different head shape and differences in facial structures, and the presence of syndactyly (fusion of fingers or toes).

Signs & Symptoms

Pfeiffer syndrome is a rare genetic condition that affects the development of the skull and limbs. It is characterized by craniosynostosis (premature fusion of skull bones) and syndactyly (fusion of fingers and toes).

The severity of symptoms can vary, and they are typically categorized into two subtypes:
a. Classic Pfeiffer syndrome and
b. Cloverleaf skull syndrome (a more severe form of Pfeiffer syndrome).

1. Craniofacial Characteristics (Skull and Face)

- Craniosynostosis:
  - The premature fusion of the skull bones, which affects the shape of the head. It can cause differences in skull growth and increased pressure on the brain.
  - Head differences: The skull may be shaped differently due to early fusion, leading to a wide, short skull or a tower-like appearance (a high forehead with a narrow face).
  - Wide-set eyes (hypertelorism): The distance between the eyes is often larger than normal.
  - Protruding eyes (exophthalmos): The eyes may appear to bulge outwards due to the differing skull shape.
  - Beaked nose: A nose that appears narrow or pointed.

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- Underdeveloped upper jaw (midface hypoplasia): This can cause receding cheeks, leading to a sunken face appearance.

2. Syndactyly (Fusion of Fingers and Toes)

- Fused fingers or toes:
  - A characteristic symptom of Pfeiffer syndrome is syndactyly, where two or more fingers or toes are fused together, sometimes involving both soft tissue and bones.
  - Partial syndactyly: Fingers or toes may be fused but still have some distinct features.
  - Complete syndactyly: Fingers or toes may be fully fused, creating a single, unified digit.

3. Neurological Symptoms

- Developmental delay: Children with Pfeiffer syndrome may have delayed motor skills, speech development, and intellectual disabilities, often due to increased intracranial pressure from craniosynostosis.
- Seizures: Some children may experience seizures due to brain pressure or structural differences.
- Hydrocephalus: The increased pressure in the skull can lead to fluid accumulation around the brain, causing hydrocephalus (water on the brain).

4. Respiratory and Ear Problems

- Breathing difficulties: The differences in skull and facial features can affect the development of the airways, leading to breathing problems, especially during sleep.
- Hearing loss: Due to differences in bone development, hearing loss may occur because of ear canal obstruction or middle ear problems.

5. Skeletal and Limb differences

- Syndactyly (fusion of fingers and toes) is the most notable skeletal symptom, but other limb differences such as club feet or bent limbs may be present in some cases.
- Shortened limbs or joint stiffness may occur in some individuals.

6. Vision Issues

- Vision problems can occur due to the eye sockets developing differently, including:
  - Exophthalmos (protruding eyes) or strabismus (crossed eyes).
  - Vision impairment or blindness due to optic nerve compression or structural differences.

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7. Other Possible Features

- Teeth differences: Some individuals may have impaired teeth development or early loss of teeth.
- Hearing loss: This is due to the middle ear developing differently or damage to the auditory nerve.

Pfeiffer Syndrome Subtypes

- Classic Pfeiffer Syndrome (Type 1):
  - Characterized by craniosynostosis and syndactyly, but less severe than Type 2.
  - Normal intelligence is possible, though developmental delays are common.
- Cloverleaf Skull Syndrome (Type 2):
  - A more severe form, where the skull has a cloverleaf shape due to extensive craniosynostosis, leading to severe neurological issues and life-threatening complications.
  - This form is associated with severe developmental delays, intellectual disabilities, and life-threatening conditions like hydrocephalus and breathing difficulties.

Causes (*the why*)

Pfeiffer syndrome is caused by mutations in specific genes that are involved in the development of the skull and limbs. It is an autosomal dominant genetic condition, meaning that an individual only needs one copy of the mutated gene to inherit the condition. In most cases, these mutations are sporadic, meaning they occur randomly, but they can also be inherited from a parent who carries the mutation.

1. Genetic Mutations

Pfeiffer syndrome is primarily caused by mutations in two genes:

- FGFR2 (Fibroblast Growth Factor Receptor 2)
- FGFR1 (Fibroblast Growth Factor Receptor 1)

Both of these genes are involved in the development and growth of bones and other tissues in the body. Mutations in these genes result in premature fusion of skull bones (craniosynostosis) and other characteristic features of the syndrome.

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FGFR2 Mutations (most common)

- The majority of Pfeiffer syndrome cases are caused by mutations in the FGFR2 gene. This gene provides instructions for making a protein called the fibroblast growth factor receptor 2, which helps regulate cell growth and development.
- Mutations in FGFR2 interfere with the signalling pathways that control bone growth, leading to the premature fusion of skull bones and other associated symptoms, such as syndactyly (fusion of fingers and toes).

FGFR1 Mutations

- FGFR1 mutations are much rarer but can also cause Pfeiffer syndrome, particularly in cases with more severe features. Like FGFR2, the FGFR1 gene codes for a receptor involved in bone and tissue development.

2. Inheritance Pattern

Pfeiffer syndrome follows an autosomal dominant inheritance pattern, meaning that a person only needs one copy of the mutated gene (from either parent) to develop the condition. However, the majority of cases are caused by new mutations (de novo mutations) and are not inherited from an affected parent. These new mutations occur in the egg or sperm cells or during early embryonic development.

- One affected parent with a mutated gene has a 50% chance of passing the mutation to their child.
- Sporadic cases (without a family history) can occur due to a random mutation in the FGFR2 or FGFR1 gene.

No known environmental causes: There is no evidence suggesting that environmental factors (such as toxins, infections, or dietary factors) directly cause Pfeiffer syndrome.

4. Pathophysiology (how mutations affect development)

The mutations in the FGFR2 or FGFR1 genes lead to variations in the activation of fibroblast growth factor receptor signalling pathways. This results in differences in bone growth and premature fusion of skull bones (craniosynostosis).

- Craniosynostosis: The skull bones are supposed to remain flexible during infancy to allow for brain growth. In Pfeiffer syndrome, the premature fusion of these bones can cause differences in the shape of the skull and can put pressure on the brain.
- Syndactyly: The same mutations also affect the development of fingers and toes, leading to fusion of digits (syndactyly). This occurs due to improper growth signalling in the limbs.

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The brain may also be affected by increased intracranial pressure due to craniosynostosis, leading to developmental delays, neurological complications, and in some severe cases, hydrocephalus (accumulation of fluid in the brain).

Testing & Diagnosis

Pfeiffer syndrome is diagnosed based on a combination of clinical features, genetic testing, and sometimes imaging studies.

1. Clinical Evaluation

The first step in diagnosing Pfeiffer syndrome is a clinical evaluation by a doctor. The doctor will assess the patient's medical history, perform a physical examination, and observe for specific signs and symptoms such as:

- Craniosynostosis: differences in head shape due to the early fusion of skull bones, and possible signs of increased intracranial pressure.
- Syndactyly: Fusion of fingers and/or toes.
- Facial features: Wide-set eyes, protruding eyes, beaked nose, underdeveloped upper jaw (midface hypoplasia).
- Developmental delays or neurological differences.

If these features are present, the doctor may suspect Pfeiffer syndrome and order additional tests to confirm the diagnosis.

2. Genetic Testing

- Genetic testing is essential for confirming the diagnosis of Pfeiffer syndrome. Mutations in the FGFR2 or FGFR1 genes are the cause of the syndrome, and genetic testing can detect these mutations.
  - FGFR2 gene mutations are the most common cause, but FGFR1 gene mutations can also cause the syndrome.
  - Genetic testing can be performed through a blood test or a buccal swab to analyse the patient's DNA.
- Next-generation sequencing (NGS) or whole exome sequencing (WES) can be used to detect mutations in the FGFR2 or FGFR1 genes. If a mutation is detected, this confirms the diagnosis of Pfeiffer syndrome.
- Genetic counselling is recommended for families, as it can help explain the inheritance pattern and provide information on recurrence risks for future pregnancies.

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3. Imaging Studies

Imaging studies, such as X-rays, CT scans, or MRI, are often used to evaluate the extent of craniosynostosis and facial differences, as well as to check for other complications like hydrocephalus. These imaging techniques help assess the skull and brain development, detect skull differences, and identify any pressure on the brain.

- X-rays: To observe the fusion of skull bones.
- CT scan: More detailed than an X-ray, it can give a clearer picture of the skull shape and the degree of craniosynostosis.
- MRI: Can be used to assess brain development, monitor for hydrocephalus, or evaluate other neurological issues.

4. Evaluation of Associated Complications

In some cases, further testing may be necessary to evaluate any complications associated with Pfeiffer syndrome:

- Neurological testing: To assess any developmental delays, intellectual disabilities, or seizures. This might include neurological assessments or electroencephalograms (EEGs) for detecting seizures.
- Ophthalmologic evaluation: If there are issues like exophthalmos (protruding eyes) or vision impairment, an eye doctor may assess the eyes and optic nerve.
- Hearing tests: If there is suspected hearing loss, testing by an audiologist may be performed.

Treatment

Pfeiffer syndrome is a genetic condition with no cure, and treatment is focused on managing symptoms, improving quality of life, and addressing complications. The approach to treatment is often multidisciplinary, involving a team of specialists including paediatricians, geneticists, neurosurgeons, craniofacial surgeons, and orthopaedic surgeons. The specific treatment plan depends on the severity of the symptoms and the subtype of Pfeiffer syndrome (classic or Cloverleaf skull syndrome).

1. Surgical Interventions

Craniosynostosis Surgery

- Craniosynostosis (the premature fusion of skull bones) is one of the characteristic features of Pfeiffer syndrome, leading to differences in the shape of the skull and increased pressure on the brain. Surgery is often necessary to relieve intracranial pressure and allow for normal brain growth.

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- Cranial vault remodelling surgery is performed to reshape the skull and prevent brain damage. It typically involves removing and reshaping sections of the skull and then reattaching them in a more normal position.
- The timing of surgery depends on the child's age and the severity of the craniosynostosis, but it is usually done in infancy or early childhood to maximize brain development.

Orbital Surgery

- In some cases, orbital surgeries may be performed to address exophthalmos (bulging eyes) or sunken eyes due to craniosynostosis. This can address the appearance of the face and prevent vision problems.

Facial Reconstruction Surgery

- Reconstructive surgery can be done to address severe facial differences such as a beaked nose, midface hypoplasia (underdeveloped upper jaw), or facial asymmetry.
- These surgeries aim to address aesthetic appearance and may also help with breathing or eating difficulties if the upper jaw is involved.

Syndactyly Surgery

- Syndactyly (fusion of fingers and toes) is a characteristic feature of Pfeiffer syndrome. Surgical separation of the fused fingers or toes is often recommended to improve functionality and appearance.
- This surgery is typically done after the child is older (around 6-12 months of age) to allow for healing and growth of the digits.

2. Neurological Management

- Hydrocephalus (fluid build-up in the brain) is common in severe cases of Pfeiffer syndrome due to increased intracranial pressure. If hydrocephalus develops, the child may require shunt placement to drain the excess fluid and reduce pressure on the brain.
- Developmental delays and neurological issues (such as seizures) may be managed with therapy and medications.
  - Physiotherapy and occupational therapy can help with motor skills and coordination.
  - Speech therapy may be needed to address communication difficulties.
  - Anticonvulsant medications may be prescribed for seizure management.

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3. Breathing and Sleep Support

- Due to craniofacial differences, some children with Pfeiffer syndrome may experience breathing difficulties, especially during sleep.
  - Sleep apnoea is common, and treatment may involve the use of a CPAP machine (Continuous Positive Airway Pressure) to help keep the airways open during sleep.
  - Surgical interventions to address facial and airway differences may also be necessary to improve breathing.

4. Vision and Hearing Support

- Children with Pfeiffer syndrome may experience vision problems due to eye anomalies or increased intracranial pressure.
  - Regular eye exams by an ophthalmologist are essential to monitor for vision loss or eye movement issues.
  - If vision impairment is detected, appropriate corrective measures, such as glasses or surgery, may be recommended.
- Hearing loss is another concern, often due to middle ear problems caused by facial differences.
  - Hearing tests should be performed early in life to identify any hearing issues. If hearing loss is detected, options like hearing aids or cochlear implants may be considered.

5. Genetic Counselling

- Because Pfeiffer syndrome is a genetic condition, families with an affected child may benefit from genetic counselling.
  - Genetic counselling can provide families with information about the inheritance pattern, the risk of recurrence in future pregnancies, and the options for prenatal testing in future pregnancies.

6. Psychological and Social Support

- The physical and cosmetic effects of Pfeiffer syndrome can have a significant impact on a child's emotional and social well-being. Psychological support, including counselling or therapy, can help the child and family cope with the challenges of the syndrome.
  - Support groups or connections with other families affected by Pfeiffer syndrome can also provide valuable emotional support and shared experiences.

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7. Ongoing Monitoring

- Regular follow-up appointments with specialists are crucial for managing the condition and detecting complications early. This may include:
  - Neurological assessments to monitor for developmental delays and potential neurological issues.
  - Orthopaedic care to address limb anomalies such as syndactyly.
  - Routine imaging (e.g., CT or MRI scans) to monitor skull growth and check for hydrocephalus or other complications.

With appropriate surgical interventions, supportive therapies, and monitoring, many children with Pfeiffer syndrome can lead fulfilling lives, though the condition requires careful management to ensure the best outcomes.

Did you know?

In Australia, approximately 1 baby per 100,000 births is diagnosed with Pfeiffer syndrome.*

Pfeiffer syndrome was first described in 1964 by German physician Walter Pfeiffer. He identified the condition as a form of craniosynostosis characterized by the premature fusion of skull sutures, which leads to differences in head shape and facial features.

References:

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How we can support you:

- Care packs
- Financial assistance
- Family support coordinator
- Connection to other families