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Case Report

Pfeiffer syndrome: a rare craniosynostosis syndrome – a case report

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ABSTRACT

Pfeiffer syndrome is a rare autosomal dominant disorder caused by FGFR1 or FGFR2 mutations, characterized by craniosynostosis, midfacial hypoplasia, broad thumbs and toes, and variable neurodevelopmental delay. Type I represents the milder form. In this case, a 15-month-old male presented with macrocephaly, global developmental delay, irritability, and vomiting. Examination revealed a tall head with tense fontanelles, proptosis, midfacial hypoplasia, and broad digits. CT imaging showed bicoronal craniosynostosis with hydrocephalus. Fundoscopy revealed disc edema. Genetic testing confirmed a heterozygous mutation in exon 7 of the FGFR2 gene. Management included acetazolamide and planned ventriculoperitoneal shunt insertion. The patient is under multidisciplinary follow-up for craniofacial reconstruction and neurodevelopmental support. This case highlights an atypical, late presentation of Pfeiffer syndrome Type I with raised intracranial pressure and hydrocephalus. Early diagnosis and intervention, supported by molecular testing, are essential to optimize outcomes.

Keywords: Pfeiffer syndrome, Craniosynostosis, Hydrocephalus, FGFR2 mutation

INTRODUCTION

Pfeiffer syndrome (PS) is a rare autosomal dominant congenital disorder, first described by Rudolf Pfeiffer in 1964. It is characterized by craniosynostosis, midfacial hypoplasia, broad and medially deviated thumbs and great toes, and partial soft tissue syndactyly of the hands and feet. Additional features may include hydrocephalus, ocular proptosis, elbow ankylosis or synostosis, abnormal internal organs, and delayed neurodevelopment. Pfeiffer syndrome is caused by activating mutations in the fibroblast growth factor receptor genes FGFR2 or FGFR1.[1]

Clinically, Pfeiffer syndrome is divided into three subtypes based on severity. Type 1, or "classic" PS, typically presents with milder craniofacial features, normal intelligence, and a generally favourable prognosis. Type 2 is marked by a cloverleaf-shaped skull (kleeblattschädel deformity), extreme ocular proptosis, severe limb anomalies, and significant neurodevelopmental impairment. Type 3 resembles type 2 in severity but lacks the cloverleaf skull configuration.[2] The estimated incidence of Pfeiffer syndrome is approximately 1 in 100,000 live births.[3] We reported a case of a 15-month-old child with complains of craniofacial anomalies, global developmental delay and broad toes.

CASE REPORT

A male infant was born at 38 weeks of gestation via caesarean section in view of non-progression of labor following an uneventful pregnancy. At birth, his weight was 2.7 kg (25th–50th percentile), head circumference measured 34 cm (25th–50th percentile), and length was 52 cm (25th–50th percentile). Parents were a non-consanguineous couple and exhibit normal physical

features. The child is the first born and is the only one affected by the condition in the family.

At about 9 months of age, the parents noticed an abnormally large head than compared to peers. Developmental history revealed global developmental delay, with delayed attainment of motor, language, and social milestones. The child presented with increasing irritability, which was followed by vomiting. Post-emesis, the irritability showed a noticeable reduction. Anthropometric measurements revealed that the child's height and weight were between the 10th and 25th percentiles, while the head circumference was 49.5 cm (>95th percentile).

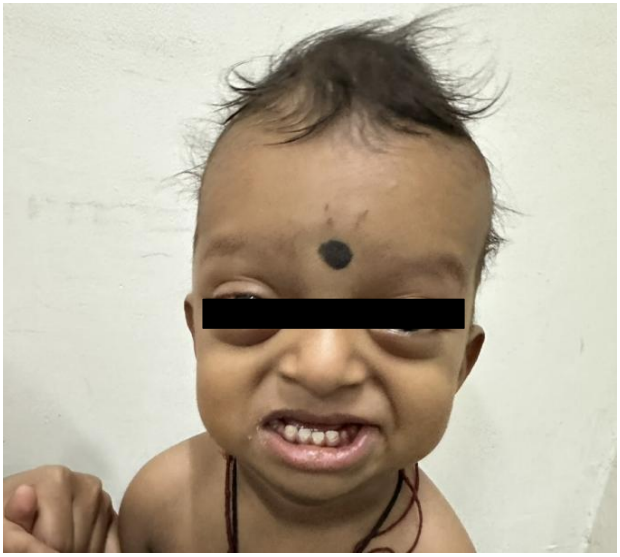

Figure 1: Tall head, hypertelorism, proptosis, mid-facial hypoplasia.

Figure 2: Bulging anterior fontanelle.

Head-to-toe examination revealed a tall skull with a bulging and tense anterior fontanelle measuring approximately 4×4 cm and an open posterior fontanelle measuring 0.5×0.5 cm. Bicoronal suture separation was noted along with prominent dilated scalp veins. Dysmorphic features included low-set ears, proptosis with hypertelorism, and midfacial hypoplasia. Examination of the extremities revealed broad fingers and toes with wide interdigital spaces. There was no deformity or limitation of movement in the bilateral elbow or shoulder joints. Neurological examination did not reveal any focal deficits. Examination of the other systems was unremarkable.

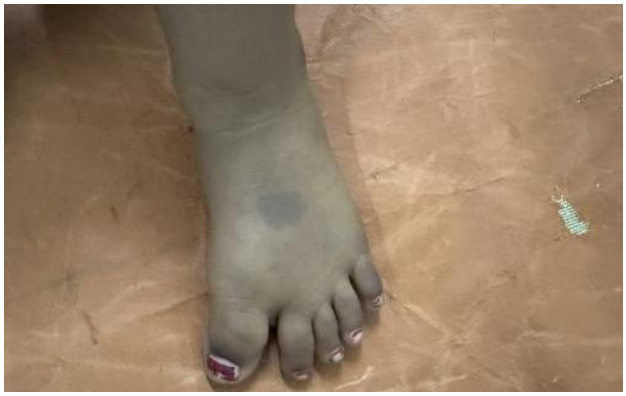

Figure 3: Broad toes and sandal gap.

Investigations

Fundoscopic examination revealed changes suggestive of chronic disc edema, characterized by pallid optic disc swelling.

Neuroimaging with computed tomography (CT) demonstrated dilatation of the bilateral lateral ventricles, indicative of hydrocephalus, along with prominence of the anterior fontanelle with evidence of complex craniosynostosis involving premature fusion of bilateral coronal sutures with scelortic margins suggestive of Pfeiffer Syndorme. MRI Brain showed features suggestive of obstructive hydrocephalus due to fourth ventricular outlet obstruction.

Management

Following the diagnosis of complex craniosynostosis with hydrocephalus suggestive of Pfeiffer syndrome, the patient was managed with a multidisciplinary team involving pediatrics, neurosurgery and ophthalmology. Due to signs of raised intracranial pressure such as irritability, tense fontanelles, and disc edema, the child was started on acetazolamide to reduce cerebrospinal fluid production. Neurosurgical evaluation led to the planned placement of a ventriculoperitoneal (VP) shunt to relieve hydrocephalus and prevent neurological deterioration. Ophthalmologic monitoring was continued for optic disc changes and proptosis-related complications. Although midfacial hypoplasia was present, the child did not require respiratory support.

Long-term management includes neurodevelopmental surveillance, audiological assessment, and craniofacial surgical planning. The child remains under regular follow-up in pediatric neurology and craniofacial clinics for ongoing monitoring and intervention.

DISCUSSION

PS is a rare autosomal dominant disorder characterized by craniosynostosis, broad thumbs and toes, midfacial hypoplasia, and variable neurologic involvement. It is genetically associated with mutations in the FGFR1 and FGFR2 genes, with FGFR2 mutations generally linked to more severe phenotypes.[4]

In our case, a male infant presented at 15 months with macrocephaly, global developmental delay, vomiting, and signs of increased intracranial pressure. Examination revealed a tall head with tense fontanelles, midfacial hypoplasia, proptosis, and broad digits. CT imaging confirmed bicoronal craniosynostosis with hydrocephalus. These findings, in the absence of cloverleaf skull or airway compromise, were consistent with Pfeiffer syndrome type I.

Genetic testing confirmed a heterozygous c.826T>G mutation in exon 7 of the FGFR2 gene, consistent with an autosomal dominant pattern. This mutation, previously reported in syndromic craniosynostoses, results in constitutive FGFR2 activation and aberrant osteoblast differentiation.[5] In our case, the molecular confirmation helped solidify the diagnosis and guide genetic counselling.

What distinguishes this case is the delayed presentation with isolated raised intracranial pressure and developmental delay, without early respiratory compromise or cloverleaf skull, which are commonly emphasized in more severe subtypes. Additionally, the presence of hydrocephalus requiring VP shunt planning is relatively less frequent in classic type I presentations. In a series by Stotland et al hydrocephalus was more commonly associated with types II and III and less frequently with the milder variant.

Furthermore, while many reported cases of Pfeiffer syndrome present in the neonatal period or within the first few weeks of life, our case presented later at 15 months with subtle but progressive symptoms, reinforcing the phenotypic variability even within the same subtype. This underlines the importance of clinical vigilance and genetic testing in atypical or delayed presentations.

Management included acetazolamide for symptom control and planned VP shunt placement to relieve hydrocephalus. Long-term care involves staged craniofacial surgeries and developmental follow-up. Early intervention has been shown to improve outcomes, particularly when initiated before 12 months of age.[6]

In summary, this case highlights the clinical heterogeneity of Pfeiffer syndrome type I, the critical role of genetic testing in diagnosis and classification, and the importance of multidisciplinary intervention. It adds to the limited literature on late-presenting, milder phenotypes with hydrocephalus, expanding the clinical spectrum of FGFR2-related craniosynostosis.

CONCLUSION

This case highlights the importance of recognizing the clinical variability of Pfeiffer syndrome, particularly in milder type I presentations with late onset of symptoms such as hydrocephalus and developmental delay. Molecular genetic testing is important to confirm the diagnosis. Management includes multiple-staged surgery of craniosynostosis, with midfacial surgery performed to reduce exophthalmos and midfacial hypoplasia. Early multidisciplinary intervention, including medical management of intracranial pressure and planned neurosurgical procedures, is essential to optimize neurodevelopmental outcomes. Continued long-term follow-up is critical for addressing craniofacial reconstruction and developmental support.

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