ORIGINAL RESEARCH PAPER

Neonatology

KEY WORDS:

PFEIFFER SYNDROME TYPE II: A GENETICALLY PROVEN CASE

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ABSTRACT

Pfeiffer syndrome is a rare genetic disorder in western population .This condition is very rare in the Asian population. This syndrome was first described by Rudolf Pfeiffer in 1964. We are presenting here is a case of newborn with pfeiffer syndrome type II demonstrating a cloverleaf skull with craniosynostosis, hypertelorism, bilateral proptosis, low set ears, syndactyly, broad thumb broad great toe, elbow synostosis.

INTRODUCTION:

Pfeiffer syndrome (PS) is a rare Genetic disorder with autosomal dominantly inherited disorder originally described by Rudolf Pfeiffer in 1964. [1] Due to the various clinical phenotypes, Cohen et al described the three subtypes. [2] Type 1 is also known as the "Classic" Pfeiffer syndrome described by Rudolf Pfeiffer who noticed the autosomal dominant inheritance pattern among families, and it is usually associated with a normal life span. Type 2 consists of "cloverleaf skull" due to extreme fusion of the skull bones, severe proptosis, finger and toe abnormalities, elbow ankylosis or synostosis. Type 3 is similar to type 2 except for the clover skull shaped deformity. Additionally, they have proptosis, visceral abnormalities (hydronephrosis, pelvic kidneys, and hypoplastic gallbladder), and severe neurological complication. To date, all cases of Type 2 and 3 have occurred sporadically, their overall prognosis being very poor with an early death. Mild variants tend to be familial and carry a relatively good prognosis.

It is caused by mutations in the fibroblast growth factor receptor (*FGFR*) genes, *FGFR1* (on chromosome 8p11.2 p11), and *FGFR2* (on chromosome 10q26) that promotes early maturation of bone cells in a developing embryo and the premature fusion of bones in the skull, hands, and feet. [2] Pfeiffer syndrome has been found to be associated with anomalies of the upper airway which can lead to midface hypoplasia, secondary nasal obstruction, choanal atresia, and tracheal anomalies. [4, 5, 6] Eye features in severe forms include shallow orbits, severe proptosis, cyclotorsion of the orbits, strabismus, and optic nerve compression from increased intracranial pressure. [7] There are few cases reported in African patients with other subtypes of Pfeiffer syndrome. To the best of our knowledge very few cases are reported form India. Molecular genetic testing is important to confirm the diagnosis.

Case report:

We report a case of a neonate a Preterm (35 weeks Gestation), Male baby appropriate for gestational age, born to Primigravida mother by lower segment caesarean section (LSCS) In view of non-onset of labour and fetal distress. Anomaly scan suggestive of occipital encephalocele. Baby was not cried immediately required resuscitation at birth, weighing 2.5 kg (25^{th}-50^{th} centile), occipitofrontal circumference was 34 cm (25^{th}-50^{th} centile) and length was 50 cm (50^{th} centile).This baby was first born baby with non-consanguineous marriage and both parents were physically normal .

Postnatally baby was shifted to NICU for post resuscitation care. He had unstable cardiopulmonary status. Baby had dysmoprphism in form of cloverleaf skull (figuer1), craniosynostosis, encephalocele, hypertelorism, bilateral proptosis, low set ears, syndactyly, broad thumb (figure2), and broad great toe(figure 3) elbow synostosis (figure 4) suggestive of syndromic association. Ultrasonography skull was done suggestive of occipital encephalocele. USG abdomen was normal. 2 D echocardiography was suggestive of small patient ductus arteriosus. Infantogram was suggestive of craniosynotosis with bilateral elbow synostosis. Genetic study reported as heterozygous, fibroblast growth factor receptor 2 (FGFR 2) mutation on the long arm of chromosome 10 suggestive of Pfeiffer syndrome type 2. Baby expired within 24 hours of life.

Figure 1 cloverleaf skull

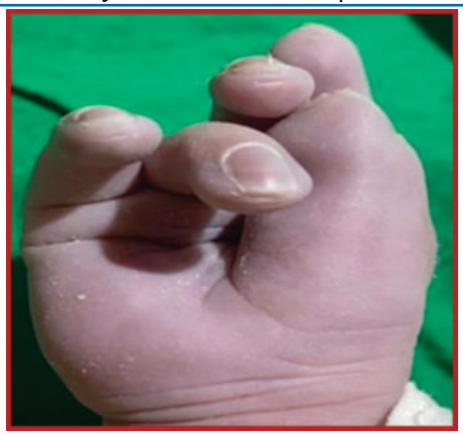

Figure 2 : Broad thumb

Figure 3 : Broad great toe with syndactyly

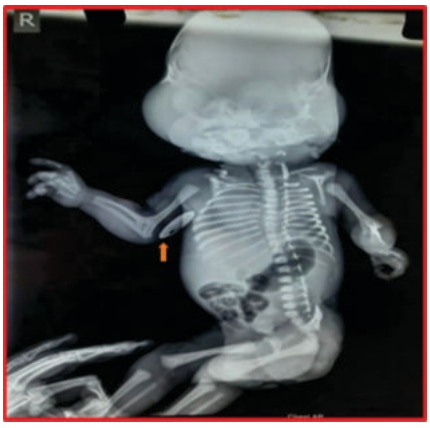

Figure 4 : Infantogram suggestive of craniosynotosis with elbow synostosis

DISCUSSION :

The exact incidence of PS is unknown, but is expected to be 1 in every 100,000 births in the Western population, and approximately 60 cases to date have been reported in the past world-wide literature. [8, 9] However, it is rarer in Asian population: only several cases were reported in Japan and few cases reports as yet in India. Cohen in 1993 classified this syndrome into 3 clinical subtypes and suggested that these subtypes might not be classified as separate entities, even though these classifications have important diagnostic and prognostic implications. Our patient had clinical findings consistent with Pfeiffer syndrome (PS) type 2, which consists of cloverleaf skull deformity due to extensive craniosynostosis, hand and foot anomalies like elbow synostosis , encephalocele, hypertelorism, bilateral proptosis, low set ears, syndactyly, broad thumb , and broad great toe . FGFR2 gene mutation is associated with severe midface hypoplasia and exorbitism. Similar mutation in the fibroblast growth factor receptor gene have been identified in Crouzon, Jackson-Weiss and Pfeiffer Syndrome types 2 and 3, thereby resulting in variable expression with distinct phenotypes. [7 , 9 ,10]. Sporadic cases have been related to advanced paternal age, and there has been speculation that older men are more susceptible to a variety of germline mutations. [11] Depending on ultrasound findings like head shape, facial and hand abnormalities prenatal diagnosis of PS type 2 can be made antenatally. Unfortunately due limited expeerience in corrective surgery of multiple major anomalies, prognosis and outcome of PS Type 2 is not good.

CONCLUSION :

The overall outcome depends on the clinical subtype of Pfeiffer syndrome. The prognosis in our patient was very poor due to various factors from labor complication. Genetic counseling should be done to parents as familial cases have a risk of recurrence.

REFERENCES

1. Pfeiffer RA. Dominant hereditary acrocephalosyndactyly. J Pediatr. 1964;90(4):301 320. [Google Scholar]
2. Cohen MM. Pfeiffer syndrome update, clinical subtypes, and guidelines for differential diagnosis. Am J Med Genet. 1993;45(3):300 307. [Abstract] [Google Scholar]
3. Schell U, Hehr A, Feldman GJ, et al, Mutations in FGFR1 and FGFR2 cause familial and sporadic pfeiffer syndrome. Hum Mol Genet. 1995;4(3):323 328. [Abstract] [Google Scholar]
4. Wenger TL, Dahl J, Bhoj EJ, et al, HHS public access. Genet Med. 2018;19(1):62 68. [Europe PMC free article] [Abstract] [Google Scholar]
5. Tan HY, Anuar NAM, Sawali H. Bilateral choanal stenosis in a craniosynostosis child: a case report. Int J Otorhinolaryngol Head Neck Surg. 2018;5(1):184. [Google Scholar]
6. Hockstein NG, Jacobs IN, Bartlett S, McDonald McGinn D, Zackai E, Huff DS. Tracheal anomalies in Pfeiffer syndrome. Arch Otolaryngol Head Neck Surg. 2004;130(11):1298 1302. [Abstract] [Google Scholar]
7. Clark JD, Compton CJ, Tahiri Y, Nunery WR, Harold Lee HB. Ophthalmic considerations in patients with Pfeiffer syndrome. Am J Ophthalmol Case Reports. 2016;2:1 3. [Europe PMC free article] [Abstract] [Google Scholar]
9. Kiyoko Oyamada M, Alonso Ferreira HS, Hoff M. Pfeiffer syndrome type 2 Case report. Sao Paulo Med J. 2003;121(4):176 179. [Abstract] [Google Scholar]
10. Herman TE, Siegel MJ. Perinatal / neonatal casebook Pfeiffer Syndrome, Type II. J Perinatol. 2001;21:565 567. [Abstract] [Google Scholar]
11. Glaser RL, Jiang W, Boyadjiev SA, et al. Paternal origin of FGFR2 mutations in sporadic cases of Crouzon syndrome and Pfeiffer syndrome. Am J Hum Genet 2000;66(3):768-77.
12. Benacerraf BR, Spiro R, Mitchell AG. Using three-dimensional ultrasound to detect craniosynostosis in a fetus with Pfeiffer syndrome. Ultrasound Obstet Gynecol 2000;16(4):391-4.