PFEIFFER TYPE I SYNDROME: A GENETICALLY PROVEN CASE REPORT

Sh. Salehpour MD, MPH [1]
S. Saket MD [2]
M. Houshmand Ph.D [3]

Abstract

Objective

Pfeiffer Syndrome is as rare as Apert syndrome in the Western population. This condition is very rare in the Asian population. At the best of our knowledge this is the first genetically proven case report from Iran. The authors report with a review of literature, the case of a infant with Pfeiffer syndrome, manifested by Lacunar skull, ventriculomegaly, bicoronal craniosynostosis,frontal bossing, shallow orbits, parrot-like nose, umbilical hernia, broad and medially deviated great toes.

Keywords: Acrocephalosyndactylia, Craniosynostoses, Broad and great toes, Pfeiffer, Syndrome

1. Assistant Professor of Pediatric Endocrinology and Metabolic diseases, Genomic Research Center,Shahid Beheshti Medical University
2. Pediatric senior resident, Genomic Research Center
3. Ph.D. of Molecular Genetics, Genetic Department of Special Medical Center, National Institute of Genetic Engineering & Biotechnology

Corresponding Author:
Sh. Salehpour MD
Mofid Children's Hospital
Mobile: +98 9121792477
E-mail: Shadabshadab@yahoo.com

Introduction

Pfeiffer syndrome (PS) is a rare autosomal dominant congenital disorder, originally described by Pfeiffer in 1964, and is characterized by an acrocephalic skull, regressed midface, syndactyly of hands and feet, and broad thumbs and big toes, with a wide range of variable severity(1-6). PS is known to be caused by mutations in exons IIIa or IIIc of the fibroblast growth factor receptor (FGFR) 2 or FGFR 1 gene(7-10). We report with a review of literature, probably the first infant in Iran with genetically proven PS who had bicoronal craniosynostosis, frontal bossing, shallow orbits, parrot-like nose, umbilical hernia, broad and medially deviated great toes.

Case Report

A male infant, aged 27 months was referred to Endocrinology and Metabolic diseases clinic of Mofid Children's hospital for further evaluation. This infant was born from a 17-year-old healthy primigravid Iranian mother. The infant was delivered by cesarean section because of diminished amniotic fluid(oligohydramnios) at 38 weeks gestation . He was 2.9 kg in weight (10-25 percentile), the head circumference was 35 cm (25-50 percentile), and the height at birth was 50 cm (50 percentile). His parents are both phenotypically normal and nonconsanguineous.

Upon birth, the infant demonstrated bilaterally fused coronal sutures, mild proptosis, and maxillary hypoplasia. There was no deformity or motion limitation of bilateral elbows or shoulder joints. The infant demonstrated evidence of icterus and need for phototherapy in neonatal ward for 3 days.

At four months of age, the infant was referred to neurosurgery clinic of our hospital for evaluation of macrocephaly, exophthalmia, anterior fontanel bulging and inspiratory stridor. Physical examination revealed a 5 kg in weight infant with

dysmorphic features affecting the face and great toes .The head circumference was 35 cm. The neurodevelopmental status in examination was normal.Computed tomogram (CT) studies of the cranium and skull X rays revealed craniosynostosis, frontal bossing and shallow orbits. Brain CT Scan revealed hydrocephalous, dilated frontal horn of third ventricles and normal forth ventricles. He did not have any abnormality upon abdominopelvic sonographic examination. Echocardiography was also normal. The patient had a medium pressure VP-Shunt insertion at 18 weeks of age and a sagital suturectomy at 13 months of age, and was planned for second surgical correction of craniosynostosis, followed by additional correction procedure for the craniofacial anomalies at a later date. Molecular analysis of the patient revealed a heterozygous C342R mutation in exone 10 and a missense T to C in mRNA. Further studies on such sporadic cases recommended enhancing the molecular information.

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(11,12). However, it is rarer in Asian population: only cases were reported in Japan(13,14) and in Korea(3) .

Cohen(15) 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. The classic PS is designated type I. Type II consists of a cloverleaf skull with Pfeiffer hands and feet, together with ankylosis of the elbows. Type III is similar to type II without the cloverleaf skull. In type III PS, ocular proptosis is severe, and the anterior cranial base is markedly short. Various visceral malformations have been found in association with type III [15]. Early demise is characteristic of both types II and III, which to date has been reported to occur only as sporadic cases(10,12). Clinical manifestations of this patient appeared to fit into subtype I according to Cohen's clinical classification of PS.

Pfeiffer syndrome is most often associated with turricephaly. The eyes are prominent and widely spaced, and the thumbs and great toes are short and broad. Partial soft tissue syndactyly may be evident(2,4). The etiology for this syndrome is autosomal dominant or fresh mutations in type I conditions, and sporadic in types II and III. PS is genetically heterogeneous(7,121).

Mutations of the fibroblast growth factor receptor (FGFR) gene family have been shown to be associated with phenotypically specific types of craniosynostosis(2,4). Mutations of the FGFR1 gene located on chromosome 8 result in Pfeiffer syndrome; a similar mutation of the FGFR2 gene causes Apert syndrome. Identical mutations of the FGFR2 gene may result in both Pfeiffer and Crouzon phenotypes(2,4). The human FGFR2 gene is located on long (q) arm of chromosome 10 between positions 25.3 and 26 contains 20 exons. The known mutation spectrum of FGFR2 has remained essentially unchanged since the review by Wilkie. More than 20 FGFR2 mutations that cause Pfeiffer syndrome have been identified. Several of these mutations change the number of cysteine amino acids (a particular protein buinding block) in a critical region of the FGFR2protein known as IgIII domain. The remaining mutations affect amino acids other than cysteine or result in an FGFR2 protein that is missing one or more aminoacids. These mutations appear to overstimulate signaling by FGFR2 protein, which promotes premature fusion of bones in the skull, hands and feet(14,24). These mutations are related to the old age of parents, especially the father, because these mutations are suspected to confer a selective advantage to survival of sperm(16). Usually, the parents are not affected and the risk for future children of that couple is minimal. The offspring of a patient with PS have a 50-60% chance of inheriting the syndrome due to the dominant characteristics of this gene.

Each of the genetic syndromes poses a risk of additional anomalies, including hydrocephalus, increased intracranial pressure (ICP), papilledema, optic atrophy due to abnormalities of the optic foramina, respiratory problems secondary to a deviated nasal septum or choanal atresia, and disorders of speech and deafness(2,4,6,18,19). Congenital anomalies of the upper airway are clearly an important cause of morbidity and mortality in PS type II and III but are rare in PS type I(17). PS may involve craniosynostosis that is most often of the coronal and lambdoid, and occasionally sagittal

sutures. Craniectomy is mandatory for management of increased ICP, and a multidisciplinary craniofacial team is essential for the long-term follow-up of affected children. Craniosynostosis may be surgically corrected with good outcomes and relatively low morbidity and mortality, especially for nonsyndromic infants(4). The most common features of the face are regressed mid-face and shallow orbits, which may be present at birth but sometimes become more evident as the childhood progresses. Underdeveloped maxillary bone of the face results in very shallow orbits and exophthalmos or proptosis. The shallow orbits and proptosis may lead to damage of the cornea from dryness, or exposure keratosis. Maxillary hypoplasia also results in a small larynx and pharynx behind the nose and mouth. This restricts the passage of air into the trachea and lungs and causes respiratory distress, particularly at night when snoring and snuffling can interrupt sleep. Similarly, the passage of food is restricted, and regurgitation may result in aspiration of food into the lungs(1).

The hands and feet in PS are involved to variable degree(20-22). The thumbs and big toes are broad and deviated radially. Patient may have mild soft tissue webbing of syndactyly between the second, third, and fourth digits of eitheror both hands and feet. The digits may be short and misshapen.

Other anomalies in PS could include a cleft palate, choanal atresia, tracheo- and broncho-malacia, tracheal stenosis(17), cloverleaf skull, fused vertebrae, Arnold-Chiari malformation, hydrocephalus, and imperforate anus. After birth, seizures and mental retardation may develop.

The above case presented by authors is in accordance with type I Pfeiffer syndrome, because the infant had a craniosynostosis only of bilateral coronal suture and demonstrated broad and medially deviated great toes that are characteristic of PS. The diagnosis of the Apert syndrome is appropriate rather than PS if a patient has broad thumbs and syndactyly with bony fusion(20) or syndactyly of the second, third and fourth web spaces(22). However, clinical differential diagnosis has been confusing until now in relation with genetic findings because Pfeiffer mutation has been reported to occur in a patient with Apert syndrome(23), and identical mutations in the FGFR2 gene could cause both PS and Crouzon syndrome phenotypes(24) as illustrated by the demonstration of both phenotypes of Apert and of PS in experimental mice(25). Some authors have attempted to revise the classification for Apert, Carpenter, Crouzon, Jackson-Weiss, Pfeiffer and Saethre-Chotzen syndromes on a genetic basis. Because of widely intermingling of phenotypic expressions or genetic sharing of the same mutation, as yet there is no definite evidence that phenotypic expressions correlate accurately with genetic mutations(13,23-27). This is probably because the gene that controls these expressions has not been elucidated to date(28).

The prognosis depends on the severity of associated anomalies, mainly the severity of the central nervous system compromise. Patients with type I syndrome have, in general, a good prognosis. Patients with types II and III usually expire early in infancy or childhood even though some may survive with aggressive medical and surgical management(8).

Multiple staged surgeries are the general treatment plan for patients with PS. In the first year of life it is preferred to release the synostotic sutures of the skull to allow adequate cranial volume and thus allowing for brain growth and expansion. The patient had a medium pressure VP-Shunt insertion at 18 weeks of age and a sagital suturectomy at 13 months of age and a bicoronal suturectomy at 23 months of age, the additional skull expansion surgery would be repeated as the child grows .Although significant malformation of the toes are present, usually these function adequately and do not require the surgical correction. Mid-facial advancement may be performed in order to provide an adequate orbital volume and reduce the exophthalmos, and to correct the dental occlusion to achieve appropriate functional position, but these procedures are not common in patients with PS.

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Figure 1. Frontal photograph of patient 4months after the bicoronal suturectomy, showing the proptosis but normal head circmference.

Figure 2. Lateral photograph of patient 4months after the bicoronal suturectomy, showing the proptosis.

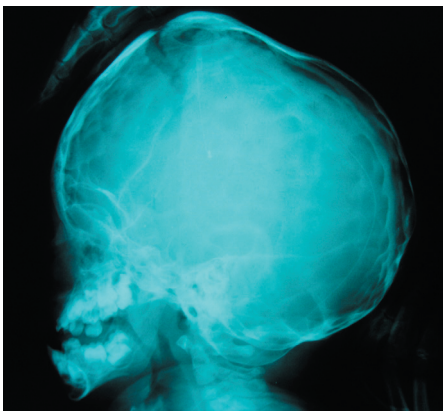

Figure 3. Skull X ray of patient 4months after the bicoronal suturectomy.

Reference

1. Pfeiffer RA. Dominant hereditary acrocephalosyndactylia. Z Kinderheilkd 1964; 90: 301-20.
2. Kenneth L Jones. Smith's Recognizable Patterns of Human Malformation.5th ed. W. B. Saunders Co;1997. P. 416-417.
3. Moon Sung Park, Jae Eon Yoo, Jaiho Chung, Soo Han Yoon. A Case of Pfeiffer Syndrome. J Korean Med Sci 2006; 21: 374-8.
4. Behrman R E,et al: Nelson Textbook of Pediatrics. 18th ed. Philadelphia:W B Saunders Company;2007. p:2456.
5. Martsolf JT, Cracco JB, Carpenter GG, O'Hara AE. Pfeiffer syndrome: an unusual type of acrocephalosyndactyly with broad thumbs and great toes. Am J Dis Child 1971;121:257-62.
6. Moore MH, Cantrell SB, Trott JA, David DJ. Pfeiffer syndrome: A clinical review. Cleft Palate-Craniofac J 1995; 32: 62-70.
7. Muenke M, Schell U, Hehr A, Robin NH, Losken HW, Schinzel A, et al. A common mutation in the fibroblast growth factor receptor 1 gene in Pfeiffer syndrome. Nat Genet 1994; 8: 269-74.
8. Robin NH, Scott JA, Arnold JE, Goldstein JA, Shilling BB, Marion RW, et al. Favorable prognosis for children with Pfeiffer syndrome types 2 and 3: implications for

classification. Am J Med Genet 1998;75:240-4.

9. Schell U, Hehr A, Feldman GJ, Robin NH, Zackai EH, de Die-Smulders C, et al. Mutations in FGFR1 and FGFR2 cause familial and sporadic Pfeiffer syndrome. Hum Mol Genet 1995; 4: 323-8.
10. Teebi AS, Kennedy S, Chun K, Ray PN. Severe and mild phenotypes in Pfeiffer syndrome with splice acceptor mutations in exon IIIc of FGFR2. Am J Med Genet 2002; 107: 43-7.
11. Goodrich JT. Craniofacial syndromes. In Principles and practice of pediatric neurosurgery. Albright AL, Pollack IF, Adelson PD, editors.New York :Thieme;1999. P.243-59.
12. Plomp AS, Hamel BC, Cobben JM, Verloes A, Offermans JP, Lajeunie E, et al.Pfeiffer syndrome type 2: further delineation and review of the literature. Am J Med Genet 1998;75:245-51.
13. Nagase T, Nagase M, Hirose S, Ohmori K. Japanese sisters with Pfeiffer syndrome and achondroplasia: a mutation analysis. J Craniofac Surg 1998;9:477-80.
14. Sakai N, Tokunaga K, Yamazaki Y, Shida H, Sakata Y, Susami T, et al. Sequence analysis of fibroblast growth factor receptor 2 (FGFR2) in Japanese patients with craniosynostosis. J Craniofac Surg 2001;12:580-5.
15. Cohen MM Jr. Pfeiffer syndrome update, clinical subtypes and guidelines for differential diagnosis. Am J Med Genet 1993; 45: 300-7.
16. Goriely A, McVean GA, Rojmyr M, Ingemarsson B, Wilkie AO. Evidence for selective advantage of pathogenic FGFR2 mutations in the male germ line. Science 2003;301: 643-6.
17. Stone P, Trevenen CL, Mitchell I, Rudd N. Congenital tracheal stenosis in Pfeiffer syndrome. Clin Genet 1990; 38: 145-8.
18. Vallino-Napoli LD. Audiologic and otologic characteristics of Pfeiffer syndrome. Cleft Palate Craniofac J 1996; 33: 524-9.
19. McCarthy JG, Glasberg SB, Cutting CB, Epstein FJ, Grayson BH, Ruff G, Thorne CH,et al. Twenty-year experience with early surgery for craniosynostosis: II. The craniofacial synostosis syndromes and pansynostosis-results and unsolved problems. Plas Recon Surg 1995;96:284-98.
20. Wilkie AO, Patey SJ, Kan SH, van den Ouweland AM, Hamel BC. FGFs, their receptors, and human limb malformations: clinical and molecular correlations. Am J Med Genet 2002;112: 266-78.
21. Martsolf JT, Cracco JB, Carpenter GG, O'Hara AE. Pfeiffer syndrome: an unusual type of acrocephalosyndactyly with broad thumbs and great toes. Am J Dis Child 1971;121: 257-62.
22. Panthaki ZJ, Armstrong MB. Hand abnormalities associated with craniofacial syndromes. J Craniofac Surg 2003;14:709-12.
23. Passos-Bueno MR, Sertie AL, Zatz M, Richieri-Costa A. Pfeiffer mutation in an Apert patient: how wide is the spectrum of variability due to mutations in the FGFR2 gene? Am J Med Genet 1997;71:243-5.
24. Rutland P, Pulleyn LJ, Reardon W, Baraitser M, Hayward R, Jones B, et a l. Identical mutations in the FGFR2 gene cause both Pfeiffer and Crouzon syndrome phenotypes. Nature Genet 1995;9:173-6.
25. Hajihosseini MK, Wilson S, De Moerlooze L, Dickson C. A splicing switch and gain-of-function mutation in FgfR2-IIIc hemizygotes causes Apert/Pfeiffer-syndrome-like phenotypes. Proc Natl Acad Sci USA 2001;98:3855-60.
26. Bae SC, Lee EH, Park MS, Hahn SH, Hong CH. A case of FGFR2 exon IIIc mutation in Crouzon syndrome. J Korean Pediatr Soc 1998; 41:1717-21.
27. Chun K, Teebi AS, Jung JH, Kennedy S, Laframboise R, Meschino WS, et al. Genetic analysis of patients with the Saethre-Chotzen phenotype. Am J Med Genet 2002;110:136-43.
28. Gripp KW, Zackai EH, Cohen MM Jr. Clinical and molecular diagnosis should be consistent. Am J Med Genet A 2003;121:188-9.