

Pfeiffer syndrome type 1: a case report and literature review

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Abstract. Pfeiffer syndrome (PS) represent a rare genetic disorder in European population that affects about 1 in 100 000 individuals. It is secondary to fibroblast growth factor receptor (FGFR) mutations resulting in premature fusion of the skull bones (craniosynostosis) and limb bones. We describe the case of a boy first evaluated at 3 weeks of life with craniaofacial dysmorphism consisting of craniosynostosis, turribrachycephaly, hypertelorism, exophthalmos and conjunctival hemorrhage, beaked nose, bilateral maxillary sinuses agenesis, choanal atresia with evidence of respiratory distress, downwardly displaced ears, impaired hearing and bilateral hydronephrosis. He also presented brachydactyly, complete syndactyly of digits I-V of the feet and partial syndactyly of digits III-IV of the hands, pollex varus and hallux varus. An extended multidisciplinary team was involved in the management of the patient and complex surgical interventions were needed: choanal calibration, correction for craniosynostosis, orthopedic correction for malformations of fingers and toes. The case reported in this paper was an exception from the classical genetic rule for PS: it was a sporadic case, not autosomal dominant inherited as commonly reported. In this case report we emphasize the importance of a multidisciplinary teamwork in order to provide the most successful plan in diagnosing and treating patients with PS.

Key Words: Pfeiffer syndrome, FGFR mutation, craniosynostosis, limb malformations, management

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Introduction

Pfeiffer syndrome (PS) is a rare genetic disorder that affects about 1 in 100 000 individuals according to the literature (Das & Winter 2020). It is secondary to fibroblast growth factor receptor (FGFR) mutations resulting in prolonged signals for osteoblasts which will lead to premature fusion of the skull bones (craniosynostosis) and limb bones (Armand T 2019). The case we report did not follow the classical genetic rule for PS: it was a sporadic case, not autosomal dominant inherited as commonly reported in the literature (Glaser 2000). It was secondary to a FGFR 2 gene mutation. An extended multidisciplinary team was involved in the management of the patient and complex interventions were needed so the patient could have a close to normal development.

Patient information

We report the case of a boy, three weeks old, second child in the family, born from a mother of 31 years old mother and a father of 42 years old father, not consanguineous, both healthy, with no history of genetic problems in the extended families. There was no prenatal suspicion of the malformation on fetal ultrasonography. The pregnancy had a normal evolution, followed by an uneventful birth. He was delivered vaginally at term, in cephalic presentation, with an Apgar score of 8 and with a birth

weight of 3830 g. At physical examination he presented normal weight, length, cranial and thoracic circumference dimensions, craniaofacial dysmorphism (fig. 1) consisting of turribrachycephaly (pyramidal skull with short and wide appearance) secondary to craniosynostosis, hypertelorism, exophthalmos and conjunctival hemorrhage, maxillary hypoplasia, beaked nose with obstruction of superior airways and of respiratory distress, downwardly displaced ears. He also presented brachydactyly, complete membranous syndactyly of digits I-V of the feet and partial membranous syndactyly of digits III-IV of the hands (fig. 2). The thumbs and halluces were wide and bend away from the other digits (pollex varus and hallux varus).

A head computed tomography (CT) scan with image reconstruction revealed premature, complete fusion of coronal suture, partial fusion of sagittal suture and secondary widening of lambdoidal and squamosal suture, a small anterior fontanel and no intracerebral lesions (fig. 3). An otorhinolaryngology consultation revealed very thin nasal fossae, choanal atresia, bilateral maxillary sinuses agenesis, vocal cords edema and congestion. Type B tympanogram was obtained at audiological examination. The ophthalmologic evaluation indicated exophthalmos with normal eye structure. Neurological examination described mild hypotonia. The abdominal ultrasonography revealed bilateral hydronephrosis. No other malformations were discovered at nephrological and cardiac assessment. Radiographs of hands



Figure 1. Turribrachycephaly



Figure 2. Membranous syndactyly of digits III-IV

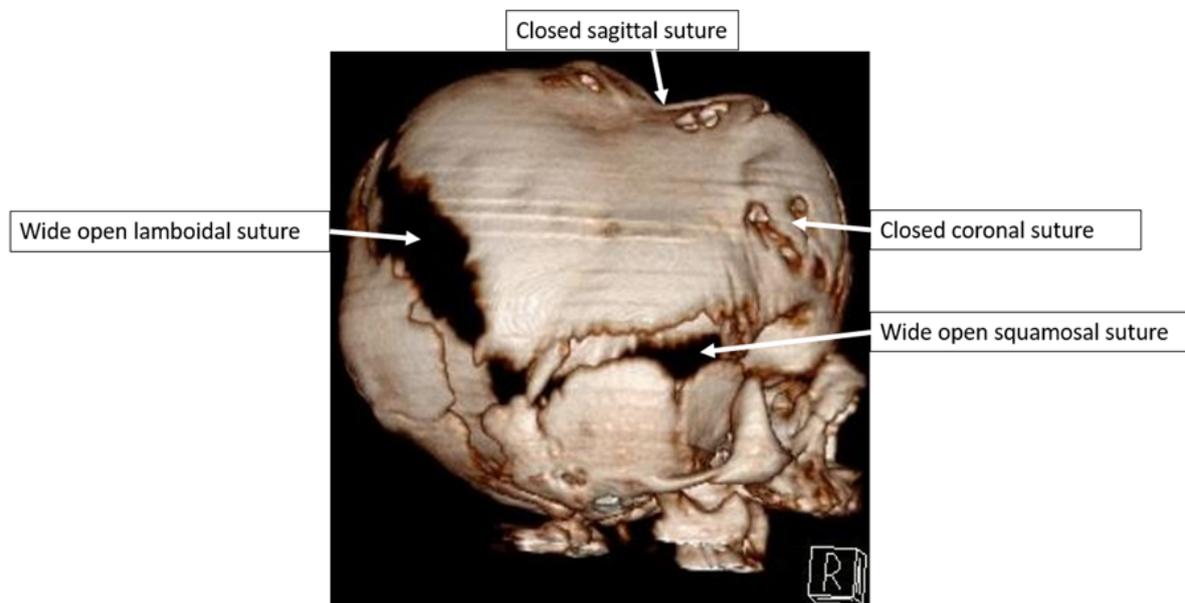


Figure 3: Head computed tomography reconstruction – neonatal period

and feet showed no bone anomalies, only membranous syndactyly. The molecular genetic testing confirmed the Pfeiffer syndrome diagnosis by detecting FGFR2 gene mutation.

Surgery for choanal calibration was performed at 3 months of age with the remission of the respiratory distress. At 6 months of age a surgical procedure for the correction of craniosynostosis was performed. Surgical correction of fingers and toes malformations was performed at one year of age. Diagnosis and genetic counseling was offered to the family. At age of 1 year and 6 months our patient had a normal psychomotor development.

Discussions

Based on the severity of the phenotype, Pfeiffer syndrome has been divided into three clinical subtypes (Sawh-Martinez & Steinbacher 2019). Type 1, known as “classic” form has mild manifestations (craniosynostoses, midface hypoplasia, beaked nose, finger and toes abnormalities like brachydactyly or syndactyly), normal neurological and intellectual development and

good outcome with a normal life span. Type 2 and 3 are more severe. Type 2 consists of cloverleaf skull due to extensive fusion of the skull bones, extreme exophthalmos, finger and toes abnormalities, elbow ankylosis or synostosis that will limit the mobility, malformations of face and airways that can lead to life-threatening problems. Type 3 differ from type 2 by the absence of cloverleaf skull. Type 2 and 3 associate neurological complications, developmental delay and poor prognosis. The main features of our patient (craniosynostosis, limbs malformations, normal neurologic developmental) oriented the diagnosis toward PS type 1. As shown in genetic studies (Koga 2012), PS type 1 is inherited in an autosomal dominant way, with just a few sporadic cases reported in literature, our case being one of those exceptions. It is caused by mutation in either FGFR1 located on chromosome 8 or in FGFR2 located on chromosome 10 as was the case in our patient (Ettinger & Williams 2013). Type 2 and 3 are caused by FGFR2 mutation, being more severe and often lead to death in infancy. They usually occur sporadically.

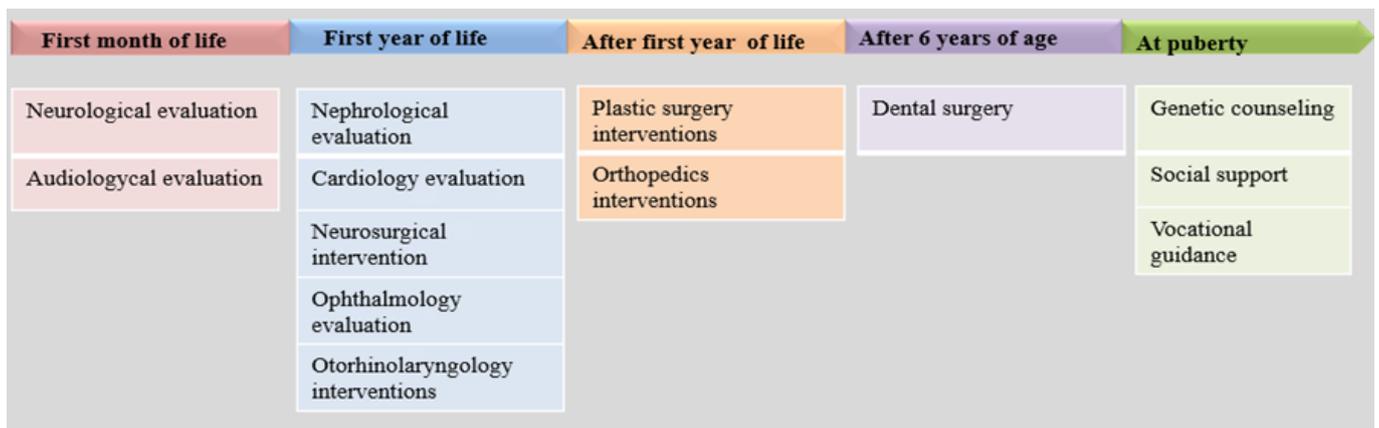


Figure 4. Timeline for specific interventions recommended in a PS case

Various studies (Su& Jin 2014, Tevan et all 2014) have showed that different fibroblast growing factors (FGF) are responsible for skull and limb bones development through binding to FGFR2. Depending on wich ligand is binding to FGFR2, two phenotypes can occur: cranial suture fusion or wider cranial sutures (Liu 2002). Our patient presented both phenotypes, as shown in fig 3: complete fusion of coronal suture, partial fusion of sagittal suture and secondary widening of lamboidal and squamosal suture.

Another aspect of the complexity of FGFR and FGF interaction is that if FGF10 (responsible for syndactyly) bind to a mutant FGFR2, the autocrine signaling will result in malformations of limbs (Sawh-Martinez & Steinbacher 2019). The same mutation of FGFR2 gene can result in different phenotypes as seen in Pfeiffer, Crouzon, Jackson-Weiss, Apert, Antley-Bixler, Beare-Stevenson cutis gyrata, Jackson-Weiss, Bent Bone Dysplasia and Seathre-Chatzen-like syndromes (Lajeunie 2006).

PS cases are asociated with parental advanced age, especialy of the father because sperm cells with this mutation have prolonged survival (Glaser et al 2000). In our case mother was 31 and father was 42.

The presented case along with literature review can provide a helpful guide in the management of PS patients (fig. 4). A multidiciplinary team has been involved in the complete assessment of the child. A correct diagnosis of the malformations is important so early interventions could be offered in order to ensure that the patient will reach his potential. Decompressive craniectomy and skull remodeling is useful in order to prevent secondary hydrocephalus. Three different types of surgery are used: early cranial vault decompression, posterior cranial vault distraction osteogenesis and fronto-orbital advancement using distraction osteogenesis. Raposo-Amaral (2020) proposed an algorithm for the surgical management of PS based on classification of severity. Neurological assessment is recommended even though type I PS do not associate neurological impairment but alterations can occur due to cranial bones commpresion over the developing brain. Intracranial volume calculated from the CT scan is a parameter that could be used for monitoring patients with craniosynostosis (Ramadat 2020) and useful for timing of neurosurgical intervention. Ophthalmological disfunctions can result from midfacial hypoplasia wich lead to oculo-orbital disproportion and exorbitism, a mild form in our case. Surgery may be needed at a young age in severe forms to prevent globe

subluxation, corneal ulceration, and potential loss of vision. The specific approach is monobloc osteotomy and distraction osteogenesis (Way 2019). Audiological evaluation, using otoacoustic emissions, pure tone audiometry or auditory brainstem response examination, is useful in determining the type and severity of hearing loss in patients with craniosynostosis as shown by Goh (2008) and Smith (2017). Alteredated tympanogram, as obtained in the case of our patient will lead to impaired language development. Congenital malformations of the upper airway related with the midface hypoplasia represent an important risk factor for an increased rate of morbidity and mortality in PS (Patel 2018). Corrective urological and cardiovascular interventions are done when required, usually in the first year of life. The orthopedic correction of the fingers and toes malformations is recommended after the first year of life when normal function is present and earlier if the function is impaired. Minimally invasive hallux interphalangeal joint arthrodesis with internal and external fixation is the recommended intervention in such cases (Flora 2018). Plastic surgery interventions are needed in some cases to correct aesthetic anomalies. Dental interventions for hypodontia, microdontia, dilacerations and radicular dentin dysplasia are sometimes recommended after definitive tooth appeared (Hassona 2017). Regarding genetic counseling, it is important for the patient to know that 50% of his offspring could inherit the mutation due to the dominant transmision pattern of the gene (Saliba2018). Special support should be offered including medical and social support, physical therapy and vocational guidance (Kutkowska-Kaźmierczak 2018).

Conclusions

A genetic mutation can manifest as multiple different phenotypes, as was the case of our patient in which a sporadic FGFR2 mutation associated a milder type of disease. In this case report we emphasized the importance of a close communication in a multidisciplinary team in order to provide the most successful plan in diagnosing and treating the patients with Pfeiffer syndrome.

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