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Case Report

# Kleeblattschädel in Pfeiffer syndrome type II

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ABSTRACT

Pfeiffer syndrome is an uncommon autosomal dominant disorder that results in craniosynostosis of multiple calvarial sutures with resulting abnormal facies and turribrachycephaly. Presented here is a case of Pfeiffer syndrome type II demonstrating a cloverleaf skull configuration and multiple facial and skull base abnormalities characteristic of the disorder. The constellation of findings consistent with Pfeiffer syndrome type II described here provides imaging depictions helpful to the radiologist who may be able to suggest genetic testing for this disorder.



## Introduction

Pfeiffer syndrome is a form of pansynostosis of the cranial sutures with associated limb abnormalities. The syndrome was first described by Rudolf Pfeiffer in 1964 [1]. There are 3 types of Pfeiffer syndrome with type I ("classic" Pfeiffer syndrome) being the mildest form of the disorder. Mid-face hypoplasia and abnormal skull shape are minimal in this form of the disease, and intelligence is more likely to be normal in these patients [2]. Type II is more severe and results in the formation of a "cloverleaf" skull, also known as kleeblattschädel, and the degree of cranial abnormality is more pronounced. Pfeiffer syndrome type II is commonly fatal in infancy [3] due to its marked compression on the intracranial structures. Pfeiffer syndrome type III is also more severe than Pfeiffer syndrome type I; however, the cloverleaf skull phenotype is less common in Pfeiffer syndrome type III [4].

The estimated incidence of all types of Pfeiffer syndrome has been estimated to be 1 per 100,000 [5], with Pfeiffer syndrome type II representing a subset of this population. Making the diagnosis is important because of its implications for prognosis and potential treatment. Presented here is a rare case of this disorder with imaging findings that nicely characterize this uncommon disease.

## Case Report

A newborn Hispanic female underwent CT of the head during the first week of life following transfer from an outside

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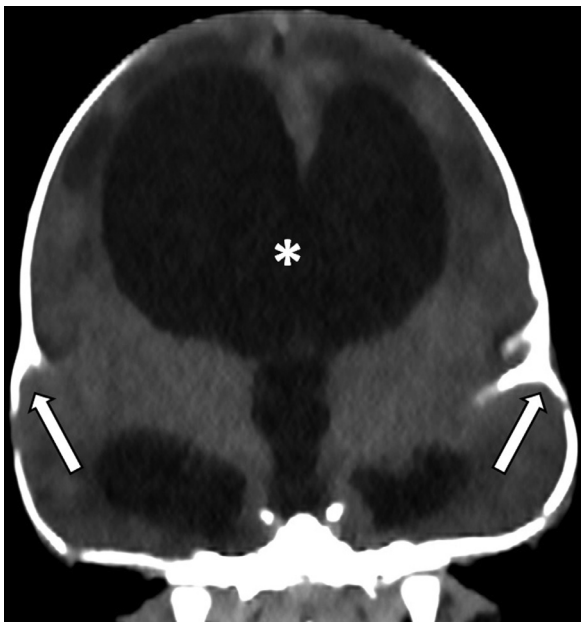

**Fig. 1 – Coronal reformatted image of a CT of the newborn female demonstrates a cloverleaf configuration of the skull (white arrows). The ventricles are markedly enlarged (asterisk).**

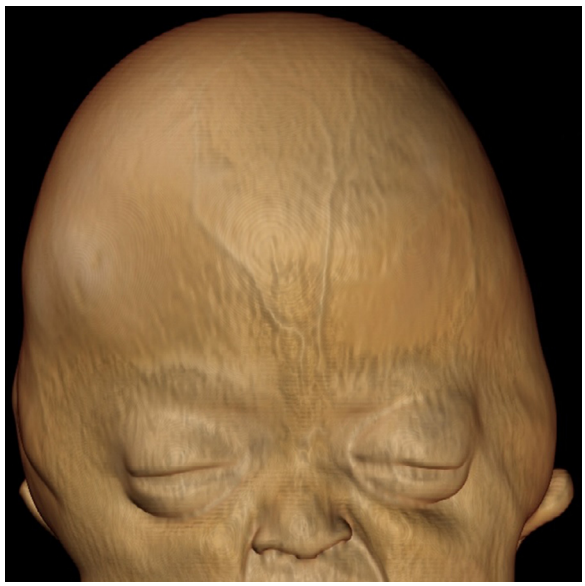

**Fig. 3 – Three-dimensional reformatted image of the skin surface from the CT in Fig. 1 viewed from the anterior depicts the typical facial characteristics of Pfeiffer syndrome type II with bilateral proptosis, a towering forehead, and prominent veins.**

hospital to evaluate an abnormal head shape. The child had been born at term; however, no prenatal history was available. There was no family history of Pfeiffer syndrome or any genetic disorder related to craniosynostosis. CT of the head showed a cloverleaf configuration of the cranium (kleeblattschädel) and marked ventriculomegaly (Fig. 1). There was pansynostosis of the cranial sutures with resulting turribrachycephaly (Fig. 2). Typical facial features of Pfeiffer syndrome type II were present including a towering forehead and bilateral proptosis, and the trilobate contour of the cranium was appreciable on physical exam (Fig. 3). Multiple vertebral segmentation anomalies were also present in the cervical spine.

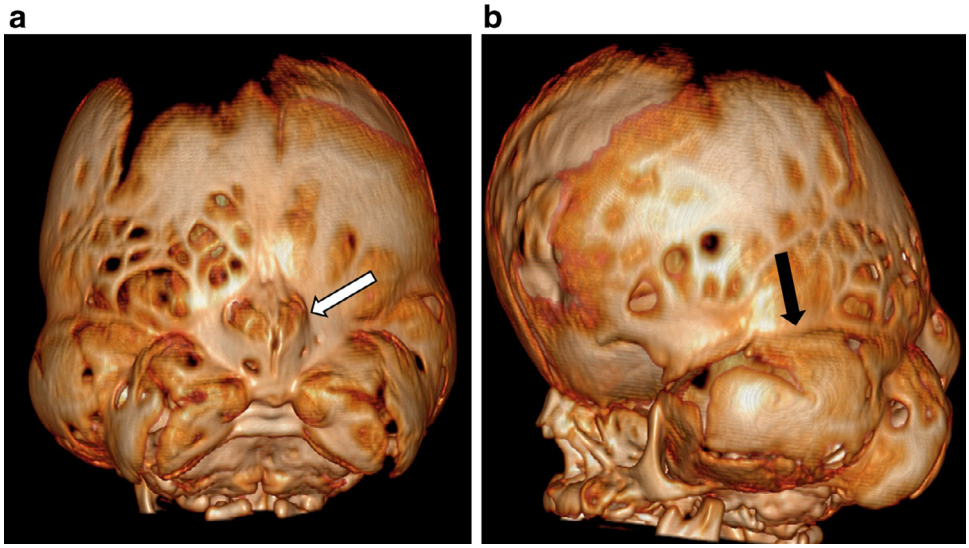


**Fig. 2 – Three-dimensional reformatted image of the CT in Fig. 1 viewed from the posterior (a) reveals craniosynostosis of the sagittal and lambdoid sutures as well as a focal protrusion of the occipital bone (white arrow). When rotated such that the anterior left aspect of the cranium is visible (b), the archetypal lateral ring of fused bone (black arrow) with temporal bulging becomes apparent.**

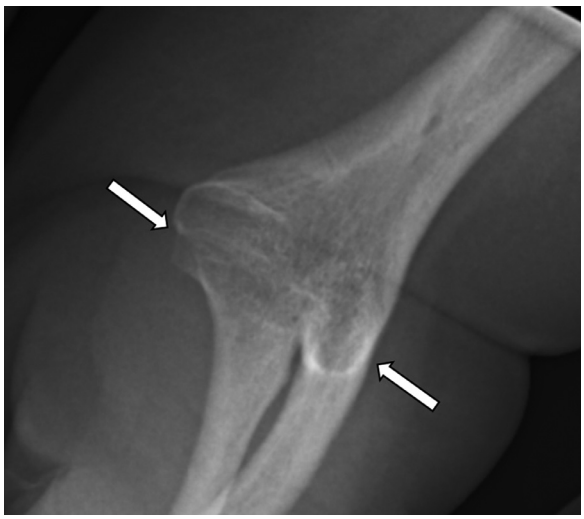

**Fig. 4 – Radiograph of the left elbow shows fusion of both the radius and ulna to the humerus (white arrows).**

A radiograph of the left elbow showed fusion of the radius and ulna to the humerus (Fig. 4). Physical exam showed brachydactyly of several digits on both hands, though the hands were not photographed or radiographed.

The patient then underwent MRI of the brain which revealed bilateral proptosis (Fig. 5), ventriculomegaly, and marked compression of the hindbrain structures (Fig. 6) with complete effacement of the prepontine cistern. Cerebellar tonsillar tissue was translated minimally below the level of the foramen magnum, and the obex was also displaced inferiorly.

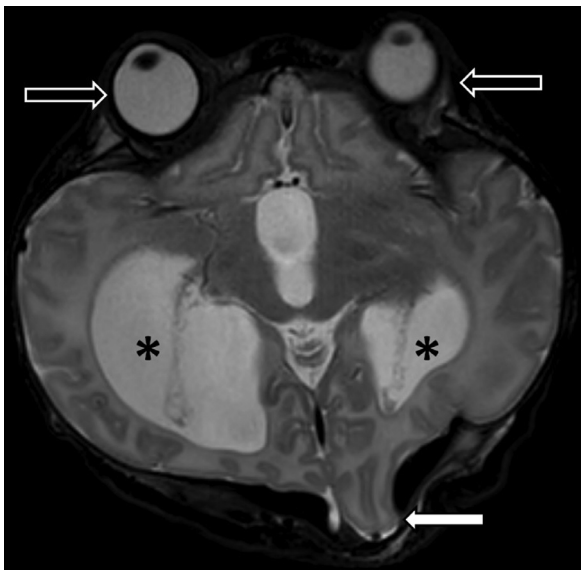

**Fig. 5 – Axial T2-weighted MRI of the brain demonstrates extension of the left occipital lobe into the space created by the calvarial protrusion (white arrow). Bilateral proptosis and hypertelorism is also noted (black arrows), and there is marked ventriculomegaly (asterisks).**

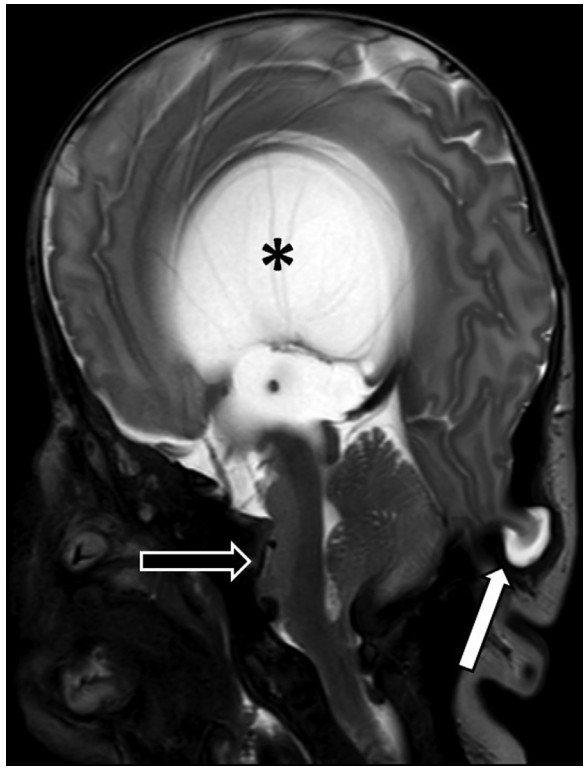

**Fig. 6 – Sagittal T2-weighted MRI of the brain reveals marked ventriculomegaly (asterisk), severe crowding of the hindbrain structures (white arrow), and extension of the left occipital lobe into the posterior calvarial protrusion (white arrow).**

Both CT and MRI depicted a midline osseous protrusion in the occipital bone. This highlights an effect of pansynostosis in which this area likely corresponds to membranous portion of the occipital bone that had not ossified at the time of sutural fusion. The brain parenchyma most likely herniated into this potential space during gestation instead, as it could not expand into the potential space that would normally be rendered by patent lambdoid and sagittal sutures.

Genetic testing confirmed the diagnosis of Pfeiffer syndrome type II. The patient's parents declined the option for palliative care and requested surgical intervention. Surgical decompression was performed following the MRI during the first week of life. The upper occipital bone was removed, and the sagittal suture was opened (Fig. 7). A follow-up CT performed 3 months following surgery confirmed new osseous growth (Fig. 8).

## Discussion

Pfeiffer syndrome type II is caused by a mutation in the gene for fibroblast growth factor receptor 2 (FGFR2) on the long arm of chromosome 10, a gene that encodes a cell membrane protein responsible for cell differentiation [6]. Pfeiffer syndrome type I has an association with FGFR1, a different gene on the

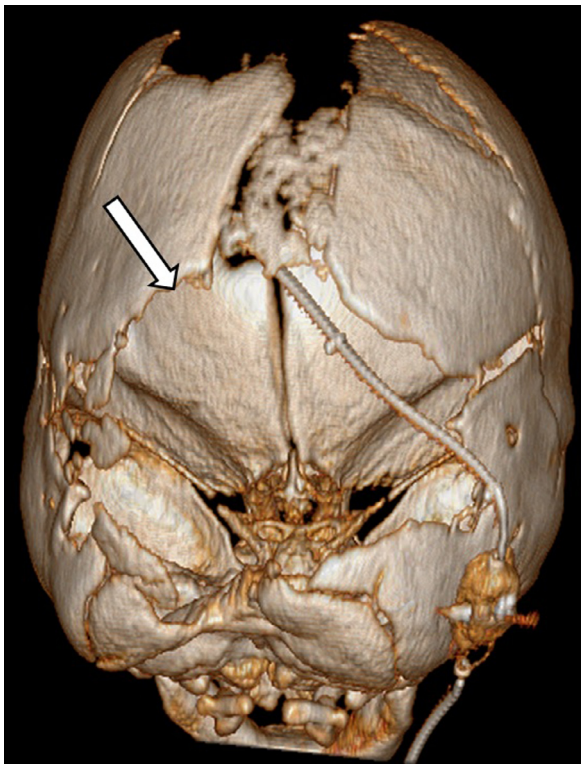

**Fig. 7 – Three-dimensional reformatted image from a CT of the head, viewed from the posterior, obtained following decompressive surgery (white arrow).**

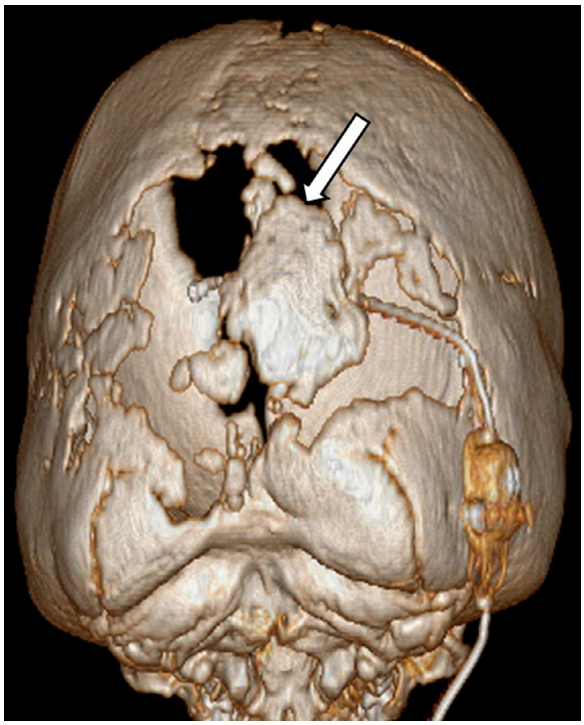

**Fig. 8 – Three-dimensional reformatted image of a CT of the head, viewed from the posterior, obtained 3 months following the CT in Fig. 7. New bone growth is apparent at the site of the decompression (white arrow).**

short arm of chromosome 8. Mutations in the FGFR genes are also implicated in Apert, Beare-Stevenson, Crouzon, Jackson-Weiss, and Muenke syndromes [7], all diseases that exhibit craniosynostosis and/or facial malformations to varying degrees. The pattern of inheritance for Pfeiffer syndrome is autosomal dominant with cases of Pfeiffer syndrome types II and III due primarily to sporadic de novo mutations [2]. Presented here is a case of Pfeiffer syndrome type II in a Hispanic child with no family history of the disease.

The cloverleaf skull deformity (kleeblattschädel) was first described by Holtermuller and Wiedemann [8]. The upper and lower leaves of the cloverleaf are formed by a ring of bone that divides the upper and lower leaves of the cloverleaf [9], and there is a honeycomb pattern of the inner vault of the skull (Fig. 2). Crowding of the posterior fossa and subsequent hindbrain herniation are common. Kleeblattschädel can be seen in severe forms of Crouzon and Apert syndromes, Saethre-Chotzen syndrome, Carpenter syndrome, and thanatophoric dysplasia, though Pfeiffer syndrome has been reported to account for approximately 15%-20% of cases [4,10]. Intellectual impairment observed in patients with cloverleaf skull is most likely a result of the intracranial mass effect from the calvarial deformity rather than an intrinsic brain abnormality, as normal intelligence by 4 years of age has been reported in some cases of patients undergoing a staged reconstruction of kleeblattschädel [11].

Surgical correction of the deformities is complex. Midface hypoplasia and choanal atresia are common, as was the case in this patient. Typical steps involved in the reconstruction include ventriculostomy or shunt placement to relieve increased intracranial pressure, fronto-orbital advancement, and posterior skull remodeling [11].

The radiologist can play an important role in the diagnosis of Pfeiffer syndrome type II. When CT findings depict kleeblattschädel in a newborn, the radiologist may recommend MRI and attention to physical examination findings that support the diagnosis of a syndromic craniosynostoses such as Pfeiffer syndrome type II.

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