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# Pfeiffer syndrome type I : A case report

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Case Report

## ABSTRACT

Pfeiffer syndrome is a rare genetic disorder characterized by various congenital anomalies such as brachycephaly, syndactyly, and craniosynostosis. This syndrome is a rare condition with a prevalence of 1 in 100,000 births. This case report discusses a seven-day-old female infant referred to dr. Soediran Mangun Sumarso Regional General Hospital, Wonogiri, Central Java, Indonesia, with Pfeiffer syndrome type 1 due to various physical abnormalities, including brachycephaly, hand and foot anomalies such as brachydactyly, syndactyly, and additional varus deformities in both feet, without any family history of similar disorders. The diagnosis of this case was made through physical examination and postnatal supporting tests. Although the prognosis for this patient is poor due to significant physical abnormalities and decreased neurological development, the outcome may still be better compared to patients with Pfeiffer syndrome types 2 and 3. The limited availability of genetic testing facilities in Indonesia hinders a more comprehensive diagnosis. Genetic testing of both parents is recommended to anticipate the risk of genetic inheritance in future pregnancies. To our knowledge, this is the first case reported in Wonogiri, Indonesia. Awareness and early detection by medical personnel play a crucial role in managing Pfeiffer syndrome, considering the rarity, complexity, and clinical variability of this condition.

## INTRODUCTION

Pfeiffer syndrome (PS) is a rare autosomal dominant genetic disorder, typically characterized by conditions such as premature fusion of cranial sutures (craniosynostosis), midfacial hypoplasia, broad and deviated thumbs, and partial syndactyly of the fingers and toes.[1] Based on its clinical manifestations, Cohen classified PS into three subtypes: type 1 (classic form), type 2 (cloverleaf skull), and type 3 (severe form without cloverleaf skull).[2]

PS is caused by mutations in the fibroblast growth factor receptor (FGFR) genes, specifically FGFR1 and FGFR2. These mutations alter receptor signaling, disrupting normal osteogenesis and cranial development.[3] One of the risk factors for PS is the father's age at conception, with an increased risk associated with advancing paternal age. Additionally, there is a genetic risk inherited from parents, with affected parents having a 50% chance of passing the condition on to their child in each pregnancy. In terms of gender, both males and females have an equal risk.[4]

The estimated incidence of Pfeiffer syndrome is approximately 1 in 100,000 live births.[5] Although extremely rare, several cases have been documented in Indonesia.[6,7] However, to the best of our knowledge, this is the first reported case of Pfeiffer syndrome in Wonogiri, Central Java. Given the rarity of the condition and the limited awareness among clinicians, this case report aims to highlight the clinical features, diagnostic challenges, and management considerations of Pfeiffer syndrome in a local healthcare setting.

## CASE DESCRIPTION

We report the case of a seven-day-old female infant who was referred to dr. Soediran Mangun Sumarso Regional General Hospital, Wonogiri, Central Java, Indonesia, due to macrocephaly, syndactyly, and various other congenital anomalies for further management. The infant was delivered via cesarean section from a 30-year-old mother at 37 weeks of gestation at Muhammadiyah Hospital, Selogiri. At birth, the infant weighed 3,300 grams, measured 50 cm in length, and had a head circumference of 36 cm. This was the mother's second child, with the first child and both parents presenting with normal clinical conditions.

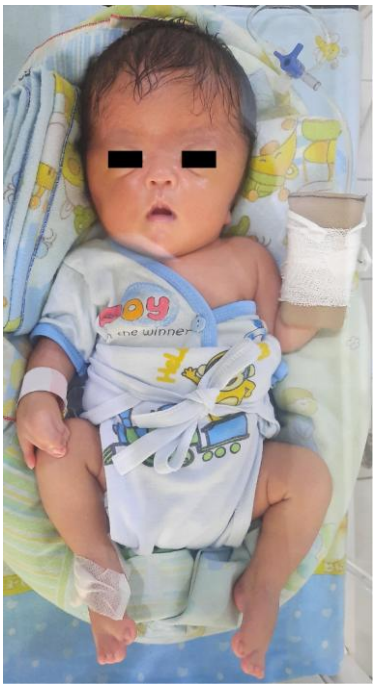


Figure 1. Clinical Photograph of the patient.

Upon arrival at Dr. Soediran Mangun Sumarso Regional General Hospital, Wonogiri, a repeat physical examination was conducted. The infant's weight was found to be 3,410 grams. The head examination revealed a brachycephalic shape with a head circumference of 38 cm, which, according to the Nellhaus chart, falls into the category of macrocephaly (Figure 1). Additionally, craniosynostosis, hypertelorism, and bilateral proptosis were observed during the head examination. The mouth examination revealed a high-arched hard palate. Examination of the upper extremities showed that both hands had two fingers with syndactyly and fused joints (Figure 2). Examination of the lower extremities revealed five toes on each foot, with syndactyly between the 2nd and 4th toes and inward deviation (varus deformity) of both feet (Figure 3). Additionally, the skin appeared to show jaundice at Kramer levels II-III. According to the parents, no similar abnormalities were found in the patient's parents or siblings. A diagnosis of Pfeiffer syndrome type 1 was established based on the clinical findings.

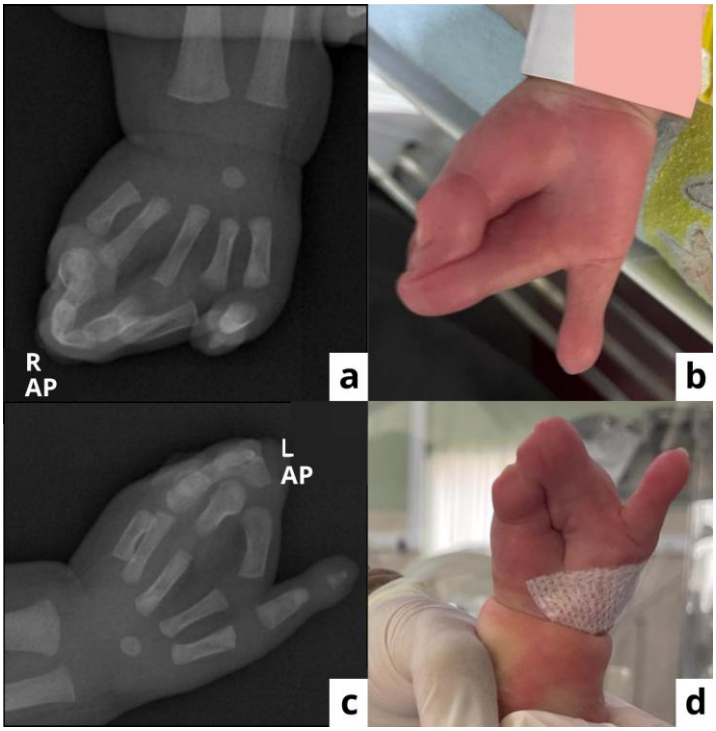

Figure 2. Photograph Manus Dextra (a) Radiological image, (b) Clinical Photograph; Photograph Manus Sinistra

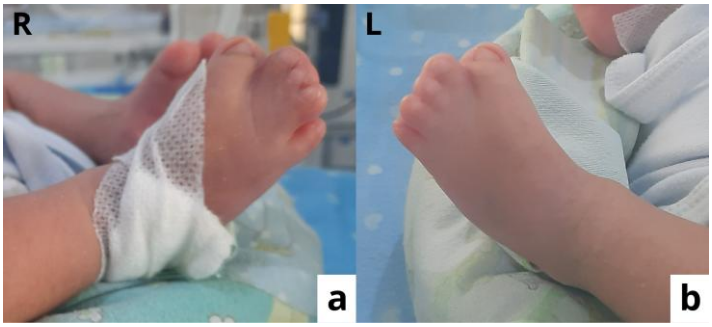

Figure 3. Clinical Photograph Pedis (a) dextra, (b) sinistra

A complete blood count revealed a low hemoglobin level of 15.7 g/dL (normal hemoglobin range is 16-25 g/dL) and an increased platelet count of 449,000/µL (normal platelet range is 140,000-440,000/µL). Other test results were within normal limits. Additionally, other blood tests showed an elevated total bilirubin level of 12.2 mg/dL (normal total bilirubin range is 0-1.2 mg/dL) and an increased direct bilirubin level of 0.4 mg/dL (normal direct bilirubin range is 0-0.2 mg/dL), indicating the presence of indirect hyperbilirubinemia.

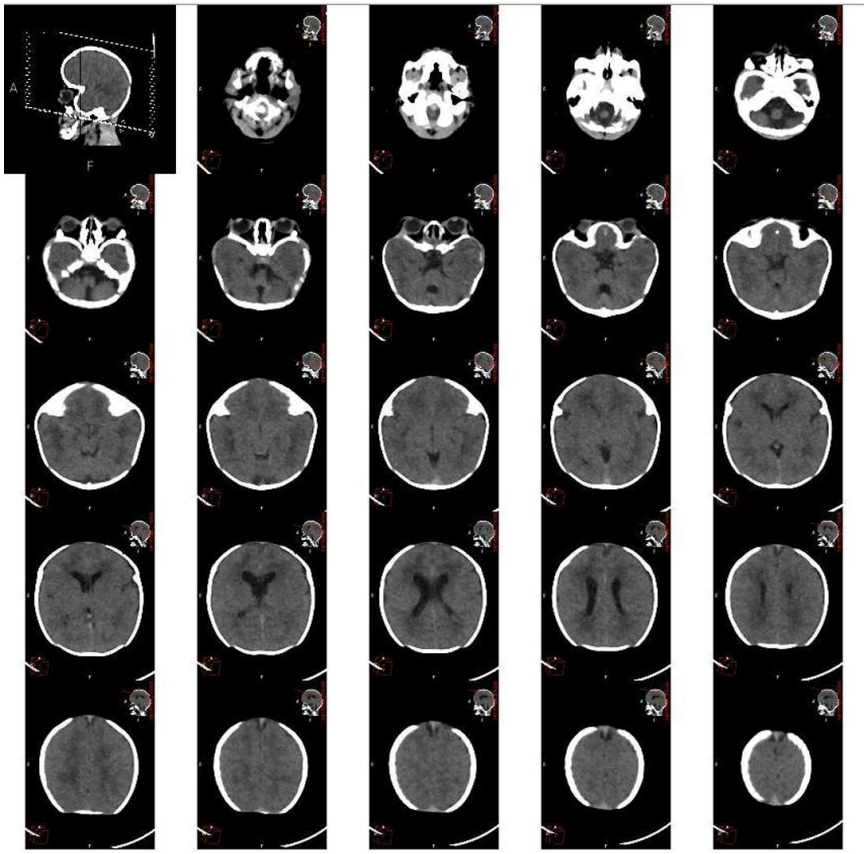

Figure 4. A non-contrast head CT scan

A CT scan offers objective anthropometric measurements to evaluate skull shape. A non-contrast head CT scan showed cephalometric results indicating macrocephaly in a child aged 0-1 year (Figure 4). However, the brain parenchyma and ventricles were within normal limits. No signs of intra- or extra-axial hemorrhage or intracranial pathological mass were observed. Genetic testing was not performed due to the limitations of the local healthcare facility, which does not offer such services.

## DISCUSSION

Pfeiffer syndrome (PS) is clinically divided into three subtypes, as described by Cohen in 1993.[2] Type 1, also known as the *classic form*, represents the mildest subtype of the disorder.[8] Its clinical features include craniosynostosis (typically brachycephaly), mild midfacial hypoplasia, and digital abnormalities such as broad and slightly deviated thumbs and great toes, with or without ocular proptosis.[9] Neurological and intellectual development are generally normal in this form, and overall prognosis is favourable.[9] Type 2 is the most severe variant, characterized by the distinctive *cloverleaf skull* deformity, severe midfacial hypoplasia, marked ocular proptosis, and digital broadening similar to Type 1 but accompanied by additional skeletal anomalies such as elbow ankylosis or synostosis.[9] This type is frequently associated with significant neurological and developmental impairment.[9] Type 3 presents with clinical features resembling Type 2, except for the absence of the cloverleaf skull deformity.[9] Although its severity is slightly lower, patients often experience substantial physical and intellectual developmental delays.[9]

The classification of the three types of PS is also related to its etiology, which involves genetic mutations. PS is associated with mutations in the fibroblast growth factor receptor (FGFR) genes, specifically FGFR1 and FGFR2.[3,8] Type I PS is typically associated with mutations in FGFR1 and FGFR2, while Type II and III PS are more commonly caused by mutations in FGFR2.[8] A mutation in FGFR1 results in a single amino acid change in the FGFR1 protein, specifically the substitution of proline with arginine at position 252 of the protein.[9] This leads to an alteration in the number of cysteine amino acids in the Ig III domain of FGFR2.[9] Mutations in FGFR1 and FGFR2

alter the function of these proteins, causing prolonged signaling, which then triggers premature fusion of cranial bones.[9] However, in some cases, mutations in these genes are not found. The absence of mutations in FGFR1 or FGFR2 does not exclude the diagnosis of PS, especially if clinical manifestations are supportive.[1]

Due to the rarity of Type 1 PS, comprehensive long-term outcome data remain limited.[10] However, available reports indicate that most affected individuals exhibit normal cognitive function and reach typical life expectancy, resulting in a generally favorable prognosis.[10] Notably, overlapping features between subtypes have been described, leading to variable phenotypic expression and prognostic diversity depending on the severity of craniofacial and skeletal involvement.[8–9]

Diagnosing PS generally involves a multidisciplinary evaluation. PS can be diagnosed both prenatally (before birth) and postnatally (after birth).[10] Prenatal diagnosis can be conducted through radiological examinations such as ultrasonography.[9] Postnatal diagnosis can be established clinically, through genetic testing, or via radiological examinations such as X-Ray, CT Scan, and/or MRI. Prenatal diagnosis is challenging through radiology alone, as some cases do not show typical signs before birth. Moreover, the absence of craniosynostosis on prenatal ultrasonography does not exclude the diagnosis of Pfeiffer Syndrome.[12]

Genetic analysis, the fibroblast growth factor receptor (FGFR) family, especially FGFR2 mutation testing, is one option that can be considered for early detection of Pfeiffer syndrome, especially if clinical signs are unclear or overlap with other craniofacial syndromes.[13,14,15] Mutations in FGFR family, are implicated in various syndromes such as Apert, Pfeiffer, Crouzon, Antley-Bixler, and Jackson-Weiss.[1,16] Notably, these FGFR mutations, FGFR1 and FGFR2 can be present across multiple syndromes.[17,18,19]

In this patient, the clinical examination is consistent with Type 1 PS, as indicated by the presence of brachycephaly, hand and foot anomalies including brachydactyly, syndactyly, and additional varus deformity in both feet. This type of PS has been reported in the literature with similar clinical manifestations in our patient.[2,8,9] Unfortunately, the diagnosis of Pfeiffer syndrome in this patient was made clinically based on physical examination and several postnatal supportive tests, without genetic testing due to limited access to such facilities. In Wonogiri, Indonesia, molecular genetic testing is still limited, so many cases of genetic disorders encountered to date have been diagnosed clinically.

Genetic testing also allows for genetic counseling for the patient's family. The disorder in this case may not be inherited directly from the parents (not autosomal dominant) but rather result from a new genetic mutation occurring in the individual. This is supported by the fact that there is no previous family history of the same disorder in the parents' lineage. Nevertheless, this genetic mutation still has the potential to be passed on in future pregnancies.[20] Genetic testing within the family allows them to understand the risk of recurrence and make informed decisions regarding future pregnancies.

The patient in this case received initial emergency treatment followed by comprehensive planning for managing the experience of complications. The emergency treatment focused on addressing the patient's feeding difficulties, which were caused by midfacial hypoplasia, leading to structural issues affecting the baby's ability to suck and swallow. Potential respiratory problems frequently encountered in PS patients, such as airway obstruction, can also result in the baby becoming quickly fatigued during feeding and having difficulty completing a feeding session. Neurological delays in PS patients can also affect the muscle coordination required for feeding. Management of these issues included positioning the baby upright during feeding to prevent aspiration and using specialized feeding bottles or nipples. Phototherapy was also administered to address the neonatal jaundice experienced by the patient. Further planning for this patient included physiotherapy to address potential global developmental delays and surgical planning to correct the extremity malformations.

Several craniosynostosis syndromes share overlapping features with Pfeiffer syndrome and should be considered as differential diagnoses.[4,21] Apert syndrome is characterized by craniosynostosis, midfacial hypoplasia, and complex syndactyly, but broad thumbs and great toes

are more typical of Pfeiffer syndrome[22]. Crouzon syndrome also presents with craniosynostosis and midfacial hypoplasia but usually lacks digital anomalies[4]. Carpenter syndrome may resemble Pfeiffer syndrome due to craniosynostosis and syndactyly, yet it can be distinguished by the presence of polydactyly, congenital heart defects, and obesity.[23] Saethre-Chotzen syndrome involves craniosynostosis and facial dysmorphism but is more often associated with ptosis, low hairline, and mild syndactyly.[21] In this case, the combination of brachycephaly, syndactyly and additional varus deformity in both feet was most consistent with Pfeiffer syndrome type I.

While this report adds meaningful insight into the clinical understanding of Pfeiffer syndrome, certain limitations should be recognized to place the findings in a proper context. This case contributes valuable insight into the clinical spectrum of Pfeiffer syndrome Type I, a rare congenital disorder that remains underreported in Indonesia. The detailed documentation of craniofacial, limb, and developmental findings enhances understanding of the phenotypic variability of this condition. Furthermore, this report emphasizes the role of clinical evaluation and multidisciplinary management in establishing diagnosis and optimizing patient care, particularly in settings with limited access to genetic testing. This report has several limitations. First, molecular genetic confirmation could not be performed due to the unavailability of *FGFR1* and *FGFR2* testing in the local setting, resulting in reliance on clinical and radiological criteria. Second, long-term follow-up data are not yet available, preventing assessment of developmental progress and long-term outcomes. Third, as a single case, the findings cannot be generalized but serve as an important reference for clinicians managing similar presentations in resource-limited environments.

## CONCLUSION

Pfeiffer syndrome, though rare, can be identified through distinctive clinical signs such as brachycephaly, syndactyly, and various other congenital anomalies. In the reported case, diagnosis via postnatal clinical examination enabled early diagnosis, although limitations in genetic testing facilities can hinder optimal management. The prognosis of the patient depends on the severity of the symptoms, with more severe types of Pfeiffer syndrome typically having less favorable outcomes. In this case, while the prognosis is better compared to Types 2 and 3, close monitoring of the patient's physical and intellectual development remains essential. Genetic testing for both parents is highly recommended to prevent the risk of genetic transmission in future pregnancies. Awareness and early detection by healthcare professionals are crucial for providing appropriate interventions and improving clinical outcomes for patients with Pfeiffer syndrome.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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## DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request. Patient-related data cannot be shared publicly due to medical confidentiality.

## SUPPLEMENTARY MATERIAL(S)

No supplementary materials are available for this article.

## AUTHORS CONTRIBUTIONS

DJP contributed to initial manuscript drafting, data interpretation, data analysis, literature review, discussion preparation, and manuscript revision. DNS contributed to clinical data collection, documentation of clinical photographs, discussion preparation, and manuscript revision. MNA contributed to clinical data collection, literature search, discussion preparation, and manuscript revision. KW contributed to patient management, clinical supervision, critical revision, and final approval of the manuscript.

## DECLARATION OF USING AI IN THE WRITING PROCESS

The authors used artificial intelligence (AI)-assisted technology only for grammar checking and editorial refinement. All analyses, interpretation of findings, and conclusions were performed independently by the authors.

## LIST OF ABBREVIATIONS

PS: Pfeiffer Syndrome; FGFR: Fibroblast Growth Factor Receptor; CT: Computed Tomography; MRI: Magnetic Resonance Imaging.

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