ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

*International Journal of Medical Science and Advanced Clinical Research (IJMACR)*

*Available Online at:www.ijmacr.com*

*Volume – 7, Issue – 6, December - 2024, Page No. : 88 – 94*

# Fanconi Anemia in A 7-Year-Old Male: A Rare Case with Multisystem Involvement

[1]Dr Sheetal Soni, Government Medical College, Kota

[1]Dr. Amrita Mayanger, Government Medical College, Kota

[1]Dr. Jitendra Jain, Government Medical College, Kota

[2]Dr. Yatendra Sahu, New Medical College and Hospital, Kota

[2]Dr. Amrit Lal Bairwa, New Medical College and Hospital, Kota

**Corresponding Author:** Dr Sheetal Soni, Government Medical College, Kota

**How to citation this article:** Dr Sheetal Soni, Dr. Amrita Mayanger, Dr. Jitendra Jain, Dr. Yatendra Sahu, Dr. Amrit Lal Bairwa, "Fanconi Anemia in A 7-Year-Old Male: A Rare Case with Multisystem Involvement", IJMACR- December - 2024, Volume – 7, Issue - 6, P. No. 88 – 94.



**Type of Publication:** Case Report

**Conflicts of Interest:** Nil

## Abstract

Fanconi anemia (FA) is mostly an autosomal recessive disorder, while it may also present as an autosomal dominant or X-linked recessive condition. Fanconi anemia is an exceedingly rare illness in India. Clinical manifestations of Fanconi Anemia (FA) encompass pancytopenia, hyperpigmentation or hypopigmentation, skeletal deformities, reduced stature or growth retardation, endocrine dysfunctions, anal atresia, hearing impairment, malignancies of the head and neck, and a familial predisposition. The diagnosis of FA can be established through clinical observations and laboratory analysis. Suggested prenatal assessments include chorionic villus sampling and amniocentesis. Androgen therapy and hematopoietic stem cell transplantation (HSCT) are suggested treatment options for Fanconi anemia (FA). Continuous monitoring of all diagnosed FA patients is required for their whole lifespan. A healthcare team with varied experience is essential for the prevention of anemia and cancer. A precise strategy and steadfast support are essential. The prognosis for FA patients is bleak due to related comorbidities. The objective of this case report is to enhance clinicians' awareness of the existence of rare diseases. A timely diagnosis accompanied by suitable therapy is essential to avert complications.

**Keywords**: Fanconi anemia, FANC gene, antenatal history, pedigree chart analysis, Hematopoietic stem cells transplant (HSCT), androgen therapy

## Introduction

Fanconi anemia, a rare autosomal recessive genetic disorder that affects all three blood cell lines. Pathogenic alleles, such as point mutations, duplications, splicing defects, and deletions, are produced by homozygous or

heterozygous mutations. Due to the cell's incapacity to perform repairs, these Fanconi anemia gene abnormalities result in a buildup of chromosomal damage. Due to these genetic mutations in the Fanconi anemia pathway, cells are unable to adequately repair DNA damage, which causes genomic instability, pancytopenia, and an increased vulnerability to UV light, cytotoxic agents, spontaneous deformation, and cancer.[1]

Patients with a family history of bone marrow failure, unbalanced translocations discovered during a diagnostic evaluation for leukemia, or signs and symptoms of pancytopenia- with or without distinctive abnormalities, should be assessed for Fanconi anemia.[2] Additionally, patients with early-onset malignancies or those experiencing severe toxicity following standard-dose chemotherapy should also be evaluated for Fanconi anemia. The chromosomal fragility test remains the gold standard for confirming a diagnosis of Fanconi anemia. The mainstays of treatment include androgen therapy, hematopoietic stem cell transplantation, and supportive care.[3]

**Patient Profile**

A 7-year-old male, born to third-degree consanguineous parents, presented with reduced height, generalized weakness, and easy fatigability. Notable physical features included prominent ear pinnae, polydactyly with an additional thumb, pigmented macules, and a high-arched palate.

Family history revealed the presence of similar phenotypic traits among relatives, along with multiple early mortalities, suggesting a possible genetic predisposition. The patient also had a history of duodenal atresia, which was surgically corrected during infancy.

On physical examination, multiple congenital anomalies and dysmorphic features were noted, consistent with a syndromic presentation.

**Case Presentation**

A 7-year-old male presented with generalized weakness, short stature, and easy fatigability. He was born (1$^{st}$ order) to third-degree consanguineous parents, raising suspicion of a genetic disorder.

**Birth and Neonatal History**

During the antenatal period, polyhydramnios was detected. The patient was born at term with a birth weight of 2.1 kg. Postnatally, he underwent surgical correction for duodenal atresia within the first 24 hours of life. His neonatal course was further complicated by pneumonia, requiring an 8-day hospital stay.

**Past Medical History**

At 6 years of age, the patient was hospitalized for dengue fever, which was confirmed serologically. During this admission, a complete blood count revealed pancytopenia. Abdominal ultrasound performed at the time incidentally revealed an absent left kidney. The patient required transfusion of packed red cells (PRC) and random donor platelets (RDP) during the course of treatment and patient recovered and discharged after 3 days.

**Family History**

A detailed family history revealed similar phenotypic traits among several relatives, consistent with autosomal recessive inheritance. Multiple instances of early mortality within the family further supported the likelihood of a genetic disorder. A pedigree chart (Figure 1) highlights the affected family members, illustrating the pattern of consanguinity-related inheritance.

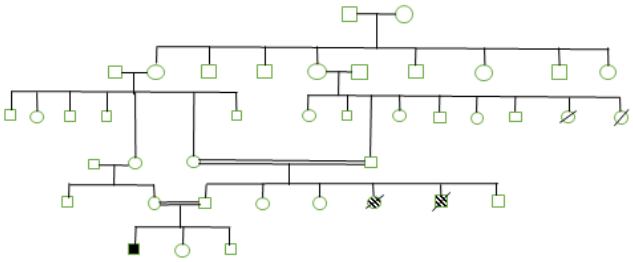

Figure 1: Pedigree Chart

**Clinical Findings:**

The patient exhibited physical features characteristic of a syndromic condition, including prominent ear pinnae, polydactyly with an additional thumb, pigmented macules, and a high-arched palate, scar mark on abdomen of operated duodenal atresia (Fig2A-E).

The child was short stature with a height of 102.2 cm that was below third standard deviation and below third standard deviation from mid parental height. The patient's upper segment to lower segment (US/LS) ratio was calculated to be approximately 1.0, which is within the normal range for their age, indicating proportionate short stature despite the reduced overall height These findings, coupled with chronic pancytopenia, heightened clinical suspicion for a genetic syndrome such as Fanconi anemia (FA).

Figure 1: Large ear pinnae

Figure 2A: Short stature

Figure 2B: Polydactyly

Figure 2C: Skin pigmentation

Figure 2D: Serrated incisors

Figure 2E:- Surgical scar

**Diagnostic Challenges:**

Initial chromosomal breakage testing, typically a key diagnostic tool for FA, was unexpectedly negative, raising the possibility of somatic mosaicism or an atypical FA variant. However, subsequent genetic testing confirmed the diagnosis, as detailed in the Investigations section

**Investigations**

1. Complete Blood Count (CBC):
   Hemoglobin: 3.7g/dl (markedly low)
   Total Leukocyte Count (TLC): 1710/mm³(low)
   Platelet Count: 49,000/mm³(low)
   Fetal Hemoglobin (HbF): 12.9%(elevated for age).
2. Peripheral Blood Film (PBF): RBC- Showing hyperchromia, macrocyte(++++), few tear drop cells seen. Occasional schistiocytes seen. Cabot ring seen RDW 15.5%
   WBC- Giant metamyelocytes observed.
3. Skeletal X-Ray (Bone Age):X-ray of the wrist (Fig 3) revealed only three carpal bones, indicating delayed bone age, approximately 2–3 years, significantly lagging behind the patient's chronological age of 7 years

Figure 3: Xray of Left hand,

4. Bone Marrow Aspirate: Dry tap observed, consistent with marrow fibrosis.
5. Bone Marrow Biopsy:

Sections revealed bony spicules.

Marrow spaces were replaced by spindle cells.

Hematopoiesis could not be appreciated.

Surrounding tissue showed areas of calcification.

Diagnosis: Possibility of Myelofibrosis.

6. Hormonal Profile: Thyroid-Stimulating Hormone (TSH): Normal levels.
7. Fundus and Neurological Examination: No abnormalities detected
8. Next-Generation Sequencing (NGS) Results: Genetic testing revealed a homozygous 5' splice site variant in intron 7 of the FANCA gene, confirming the diagnosis of Fanconi anemia

**Management and Outcome**

Following the diagnosis of Fanconi anemia, the patient was referred to a higher center for evaluation and consideration of hematopoietic stem cell transplantation (HSCT) as a definitive treatment. While awaiting a suitable donor, androgen therapy was initiated to manage bone marrow failure and reduce the need for frequent blood transfusions.

During follow-up, the patient showed a notable reduction in transfusion requirements and improvement in growth parameters, indicating a positive response to

androgen therapy. However, this therapy led to the unintended side effect of premature puberty, necessitating further evaluation and adjustments in management to balance growth and developmental outcomes.

Despite these interventions, the patient's prognosis remains guarded, given the progressive nature of Fanconi anemia. This case underscores the importance of a multidisciplinary approach and the need for early diagnosis, referral, and individualized management in improving outcomes for patients with rare genetic conditions.

**Clinical Management Challenges**

The management of Fanconi anemia (FA) is inherently complex due to its multisystem involvement. This case highlights the variable response to steroid anabolic therapy, which improved the patient's growth and reduced transfusion requirements but led to the development of premature puberty. This underscores the importance of careful monitoring to manage treatment-related side effects effectively.

The absence of a suitable bone marrow donor presents an additional challenge, as bone marrow transplantation (BMT) remains the only curative option for bone marrow failure in FA.[4] The unavailability of a donor has necessitated consideration of alternative therapeutic approaches, including potential enrollment in clinical trials for gene therapy, which represents a promising and innovative avenue for the future treatment of FA.[5]

**Genetic Considerations**

The identification of a homozygous 5' splice site variant in intron 7 of the FANCA gene in this patient is consistent with the established genetic basis of Fanconi anemia (FA), as FANCA mutations account for approximately 60-70% of FA cases. Despite this, the negative chromosomal breakage test results indicate the possibility of somatic mosaicism or an atypical presentation, underscoring the diagnostic complexities associated with FA.

These findings highlight the critical role of comprehensive genetic testing, including next-generation sequencing (NGS), in achieving an accurate diagnosis. Such advanced diagnostic tools not only confirm the presence of pathogenic variants but also provide valuable insights that guide personalized management strategies for patients with FA.[6]

**Implications of Consanguinity**

The patient's family history, marked by consanguinity and early mortality in relatives with similar phenotypic features, underscores the profound impact of genetic disorders in populations with a high prevalence of consanguineous marriages. Such familial patterns significantly increase the risk of autosomal recessive conditions, including Fanconi anemia, as seen in this case.

In these settings, genetic counseling plays a critical role. It provides families with essential information regarding recurrence risks and available preventive measures, such as prenatal diagnosis or preimplantation genetic diagnosis (PGD), to mitigate the burden of genetic diseases in future generations. Proactive genetic screening and counseling strategies can help address these challenges at both individual and community levels

**Future Directions**

Advancements in genetic research, particularly in the fields of gene therapy and novel pharmacological agents, hold significant promise for patients with Fanconi anemia (FA), especially those lacking compatible donors for bone marrow transplantation (BMT). These

innovative therapies aim to address the underlying genetic defects of FA, offering the potential to revolutionize its management.

As these approaches continue to evolve, they bring hope for more effective and personalized treatment options, reducing reliance on conventional therapies and improving long-term outcomes. The integration of these emerging modalities into clinical practice could transform the prognosis for FA patients, paving the way for a new era of tailored and targeted care

**Conclusion**

This case of Fanconi anemia (FA) in a 7-year-old male highlights the complexity of diagnosing and managing a rare genetic disorder with multisystem involvement. The patient's distinctive phenotypic features and bone marrow failure—coupled with a negative chromosomal breakage test—underscore the diagnostic challenges associated with atypical presentations of FA. This emphasizes the necessity for a comprehensive diagnostic approach, including advanced genetic testing such as next-generation sequencing (NGS), which confirmed the presence of a homozygous 5' splice site variant in the FANCA gene.

The management of FA remains challenging, as reflected in the response to anabolic steroid therapy, which improved the patient's growth parameters and reduced transfusion requirements. However, the onset of premature puberty as a side effect of treatment necessitated careful monitoring and adjustment of therapy. The absence of a suitable bone marrow donor, which remains the only curative option for bone marrow failure, further complicates management. This limitation points to the urgent need for alternative therapies, including gene therapy, which shows promise for improving patient outcomes in the future.

The patient's family history of consanguinity, with early mortality in relatives, underscores the importance of genetic counseling in managing FA, especially in populations with a high prevalence of autosomal recessive conditions. Genetic counseling provides crucial insights into recurrence risks and can guide preventive measures, such as prenatal diagnosis or preimplantation genetic diagnosis, to reduce the burden of genetic disorders in at-risk families.

This case highlights the need for early diagnosis, personalized management strategies, and continued research into novel therapies. While current treatments offer partial benefits, they also highlight the limitations in addressing the multifaceted needs of FA patients. Continued exploration into gene therapy and other innovative approaches is essential for improving the quality of life and long-term outcomes for patients with FA.

Ultimately, collaborative efforts across genetic research, clinical care, and hematology are crucial to advancing treatments and improving the outcomes for individuals affected by this rare, complex, and challenging disorder.

**References**

1. Bhandari J, Thada PK, Killeen RB, et al. Fanconi Anemia. [Updated 2024 Jun 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
2. Gajbhiye V, Lamture Y, Gharde P *et al.* Case Report: A rare case of Fanconi anaemia [version 1; peer review: awaiting peer review]. F1000Research 2023, 12:1385
3. Green AM, Kupfer GM. Fanconi anemia. Hematol Oncol Clin North Am. 2009 Apr;23(2):193-214.

4. D'Andrea, A. D. (2010). Susceptibility pathways in Fanconi's anemia and breast cancer. The New England Journal of Medicine, 362(20), 1909-1919.
5. Ceccaldi, R., Sarangi, P., & D'Andrea, A. D. (2016). The Fanconi anaemia pathway: new players and new functions. Nature Reviews Molecular Cell Biology, 17(6), 337-349.
6. Gluckman, E., & Wagner, J. E. (2010). Hematopoietic stem cell transplantation in pediatric patients with Fanconi anemia: evolution of conditioning protocols. Pediatric Clinics of North America, 57(1), 147-170.