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An Overview of Fanconi Anemia: A Genetic Disorder

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Abstract

Fanconi Anemia (FA) is a rare genetic disorder caused by DNA repair defects due to pathogenic variants in one of 21 genes. It is the primary cause of inherited bone marrow failure, marked by pancytopenia. Clinically, Fanconi Anemia (FA) is associated with congenital malformations in multiple systems, resulting in progressive bone marrow failure and heightened cancer risk, especially in the urogenital region and the head and neck. There are approximately 20 FA-related genes, but not all are impacted by mutations. These genes play a critical role in protecting against DNA damage accumulated over a lifetime. Fanconi anemia affects about 1 in 136,000 newborns, with an incidence of 1 in 100,000 to 250,000 births Mutations in three particular genes—FANCA, FANCC, and FANCG—are responsible for 80% to 90% of cases of Fanconi Anemia (FA). Clinical symptoms typically manifest in early childhood or young adulthood, with signs at birth including growth deficiencies, skeletal anomalies, small head or eyes, and abnormal skin pigmentation. In young children, symptoms can include unexplained fatigue, frequent infections, recurrent nosebleeds, easy bruising, blood in stool or urine, and other haematological issues. Several disorders linked to Fanconi Anaemia (FA) include Diamond Blackfan Anemia (DBA), Paroxysmal Nocturnal Hemoglobinuria (PNH), Schwachman-Diamond Syndrome (SDS), and Bloom Syndrome (BS). Diagnostic assessments involve array comparative genomic hybridization (array-CGH), cytogenetic testing, and molecular testing. Treatment options include oral androgen administration, recommendations for hematopoietic stem cell transplantation (HSCT), vitamin D supplementation, various therapies, hearing aids, blood transfusions, and genetic counselling.

Keywords: Fanconi anaemia (FA), FANCA, FANCC, FANCG, schwachman – diamond syndrome (SDS), and bloom syndrome (BS), Array comparative genomic hybridization (array-CGH)

INTRODUCTION

Fanconi Anemia (FA) is a genetic disorder characterized by cancer-related chromosomal instability and a range of clinical manifestations. It affects multiple body systems and can lead to bone marrow failure, physical abnormalities, organ defects, and an increased risk of certain cancers. FA is the primary cause of inherited bone marrow failure, marked by pancytopenia. This genetic syndrome often presents with congenital malformations across various systems, resulting in rapid bone marrow failure and heightened cancer risk, especially in the urogenital area and the head and neck. Most cases arise from biallelic mutations in one of the 22 genes associated with the FA/BRCA DNA repair pathway, with symptoms typically emerging at birth or in early childhood (between 5 and 10 years old). FA is a complex and chronic illness that can be psychologically challenging, with an incidence of approximately 1 in 131,000 births [1–3].

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Definition

Fanconi Anaemia (FA) is a genetic bone marrow failure syndrome characterised by pancytopenia,

leads to malignancy, and physical changes, including malformation belonging to VACTERL-H or multiple anatomical defects, (Vertebral, Anal, Cardiac, Tracheoesophageal fistula, Oesophageal atresia, Renal, upper Limb, and Hydrocephalus) association [4].

Aetiology

Fanconi anemia (FA) is a genetic disorder resulting from inherited mutations in a group of genes responsible for producing proteins. There are around 20 FA-related genes, but not all are affected by mutations. These FA genes play a crucial role in protecting against DNA damage that occurs over a person's lifetime. When these genes are mutated, the proteins that typically repair everyday DNA damage fail to function properly, leading to inadequate repair of damaged DNA. The proteins generated by these genes are involved in a cellular mechanism referred to as the FA pathway. This pathway is activated when DNA replication is hindered due to damage, sending specific proteins to the site of the damage to initiate repair, allowing DNA replication to resume [5-9].

Epidemiology

Fanconi anemia (FA) is one of the rarest forms of anemia found across different races. It affects about 1 in 136,000 newborns, with an incidence rate between 1 in 100,000 and 1 in 250,000 births. The condition can be identified in individuals from birth to the age of 49, with the average diagnosis occurring at approximately 7 years old. Studies says that comparatively of men more than women, but in all both sexes are equal. The more cases are in African population of south Africa, sub-Saharan blacks and Spanish gitanos with rates of 1 in 40000 births. The individuals diagnosed with birth defects are found in young age. About 31 babies are born with this disease in each year. In cases of United states about 1 in every 181 people is a carrier of Fanconi anaemia [10-13].

Pathophysiology

1. Fanconi Anaemia can cause at least 15gene mutation. Protein produces from this gene or involve in the cell process which is known as FA pathway.
2. The FA pathway is activated when DNA replication, the process of creating new DNA copies, is interrupted due to DNA damage. In response, the FA pathway dispatches proteins to the damaged area to initiate DNA repair, allowing replication to resume. This pathway specifically targets a form of DNA damage called interstrand cross-links (ICLs).
3. ICLs occur when two nucleotides on opposite DNA strands become abnormally linked, hindering the DNA replication process.
4. These interstrand cross-links can result from the accumulation of toxic substances produced within the body.
5. The FA core complex activates two proteins, FANCD2 and FANCI.
6. The activation of these proteins brings DNA repair proteins to the location of the interstrand cross-link (ICL), facilitating its removal and allowing DNA replication to proceed.
7. Mutations in any of three genes—FANCA, FANCC, and FANCG—are responsible for 80% to 90% of cases of Fanconi anemia.
8. Mutations in the genes associated with the FA core complex can impair its function, disrupting the entire FA pathway.
9. As a result, DNA damage is not repaired effectively, leading to the gradual accumulation of interstrand cross-links.
10. These interstrand cross-links hinder DNA replication, ultimately causing either abnormal cell death due to the failure to synthesize new DNA or uncontrolled cell growth due to insufficient DNA repair.
11. Cells that divide rapidly, such as those in the bone marrow and developing fetus, are especially at risk.
12. The loss of these cells leads to a decrease in blood cell counts and the physical abnormalities associated with Fanconi anemia.
13. When the accumulation of DNA errors leads to unchecked cell growth, individuals may develop acute myeloid leukemia or other types of cancer (Figure 1) [14].

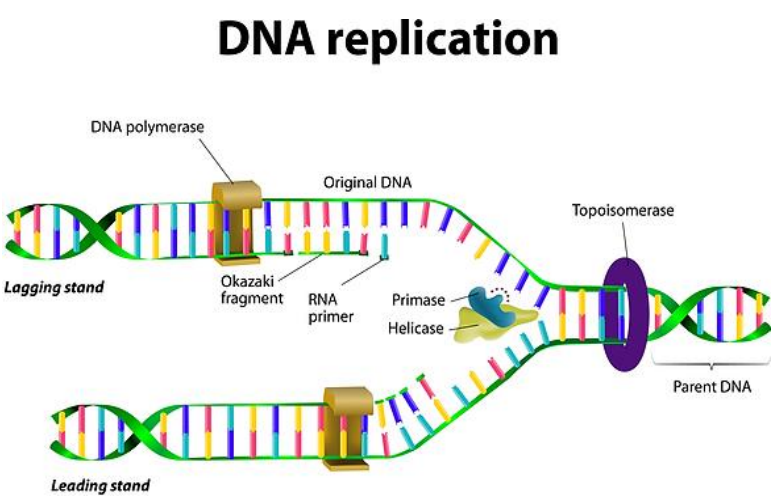

Figure 1. Pathophysiology of Fanconi Anemia.

Clinical Manifestations

Fanconi anemia can be detected at birth, in early childhood, or during young adulthood. The types and severity of symptoms can vary significantly between individuals (Figure 2) [15].

Figure 2. (a and b): Clinical Symptoms of Fanconi Anemia.

Signs and Symptoms at Birth or Early Life

- *Growth deficiency:* This may include low birth weight and short stature, either before or after birth.
- *Skeletal anomalies:* The most common include the absence of a thumb or a radius bone (one of the two bones in the forearm).
- *Abnormal skin pigmentation:* This can manifest as dark or light birthmarks.
- *Structural anomalies:* These may affect the kidneys and/or heart.
- *Small head or eyes.*
- *Gastrointestinal issues:* Problems may arise in the bowel.
- *Urinary tract abnormalities:* This includes issues with the colon or rectum.
- *Reduced size of reproductive organs in males.*

Signs and Symptoms During Childhood [16]

- Unexplained fatigue
- Frequent infections
- Frequent nosebleeds

- Easy bruising
- Blood in the stool or urine.

Haematological problem

- Petechiae
- Bruises, with later onset of pale appearance,
- Feeling tired,
- Infections,
- Low platelet count

Classic features

- Abnormal thumbs,
- Absent radii,
- Short stature,
- Skin hyperpigmentation, including café au lait spots,
- Abnormal facial features (triangular face, microcephaly),
- Abnormal kidneys, and decreased fertility.

Differential Diagnosis

A huge number of diseases seems to FA. All other blood disorder manifest Finconi anaemia and all birth defects which are associated with Fanconi anaemia should be ruled out .

1. *Diamond-Blackfan Anemia*: This is an uncommon blood disorder marked by the bone marrow's inability to produce red blood cells. Patients typically present with anemia (macrocytic-normochromic), normal platelet counts, normal white blood cell counts, and low reticulocyte levels.
2. *Paroxysmal Nocturnal Hemoglobinuria (PNH)*: PNH results from a mutation in the gene responsible for encoding the glycosylphosphatidylinositol (GPI) protein in hematopoietic cells. This mutation activates the complement system, leading to nocturnal hemolysis. Patients often exhibit anemia, jaundice, hemoglobinuria, and are at an increased risk of thrombosis.
3. *Schwachman-Diamond Syndrome (SDS)*: SDS is a rare congenital bone marrow failure syndrome characterized by a reduced white blood cell count, poor growth due to nutritional malabsorption, and in some instances, skeletal abnormalities. The main characteristics of SDS are compromised blood cell production, pancreatic issues, and a heightened risk of leukemia.
4. *Bloom Syndrome:* This rare autosomal recessive disorder is marked by genomic instability and a higher susceptibility to various cancers. Patients typically present with photosensitivity, short stature, learning difficulties, type 2 diabetes mellitus, systemic lupus erythematosus, and severe growth retardation.

DIAGNOSTIC MEASUREMENT

History Collection

- The medical history often reveals a decrease in all three blood cell lines: red blood cells (RBCs), platelets, and leukocytes.
- Symptoms such as epistaxis, petechiae, and persistent bleeding from wounds are common due to thrombocytopenia.
- Family and marital histories are crucial, especially in populations where consanguineous marriages are prevalent.

Physical Examination

- During the physical exam, the child may exhibit short stature, and over 50% of cases show light-brown skin pigmentation (often described as "café-au-lait" spots).
- Symptoms of pancytopenia may include pallor, petechiae, bruising, and cold hands or feet.

- Gastrointestinal complications, though less common, can include conditions like imperforate anus, tracheoesophageal fistula, intestinal atresia, Meckel diverticulum, megacolon, and umbilical hernia.

INVESTIGATIONS

Array Comparative Genomic Hybridization (array-CGH)

Cytogenetic Testing

Molecular Testing

Primary Prevention: Administering the human papillomavirus (HPV) vaccine to reduce the risk of gynecological cancers in females and potentially decrease the risk of oral cancer in all individuals.

Secondary Prevention: Performing T-cell depletion of the donor graft to minimize the risk of graft-versus-host disease, and using a non-radiation conditioning regimen before hematopoietic stem cell transplantation (HSCT) to lower the future risk of solid tumors.

Treatment of Manifestations

Medical treatment

- *Oral Androgen Administration:* To enhance blood counts, including red blood cells and platelets. Medications used include oxymetholone, danazol, and oxandrolone.
- Recommendations for Hematopoietic Stem Cell Transplantation (HSCT).
- Management of Growth Deficiency.
- Other anomalities like limb anomalies, ocular anomalies, renal malformations, genital anomalies, hypothyroidism, cardiac anomalies, and dermatologic manifestations as recommended.
- Advice for hearing aids may be helpful for hearing loss.
- Recommended for vitamin D supplementation.
- *Other therapies for School children are like:* - Speech, Occupational, and Physical therapy.
- Administer for blood transfusion.
- Genetic Counselling.
- Surgical treatment:
- Hand anomalies should be addressed early in life to prevent functional delays.
- Other surgeries are like congenital heart defect surgery, repair of trachea-oesophagus fistulas, and imperforate anus.
- Gene therapy.

Complications

- Haemorrhages: Oral petechial haemorrhages and spontaneous gingival bleeding are common in patients with Fanconi Anaemia and are related to the very low platelet counts.
- Infections
- *Leukemia:* Approximately it states that 9% of patients have leukemia, in 95% carry acute myeloid leukemic in which mostly are Childrens. Most of the cases can be seen in 15 to 35 years, and a progressive of 13% of 50 years.
- *Myelodysplastic syndrome:* It was reported that out of 100 patients ,7% of patients did not have leukemia but passed away due to the factor of impaired marrow function.
- *Liver Tumours:* It happened in about 45 patients, 43 of them is related with androgen use, most of aplastic anaemia or other tumours are not usually malignant. Also, high cases of solid tumours are present. Tumors frequently linked to Fanconi anemia encompass those found in the esophagus, oropharynx, vulva/vagina, brain, skin, cervix, breast, kidney, lung, lymph nodes, stomach, and colon, as well as osteogenic sarcoma and retinoblastoma. Importantly, numerous instances of oral cancer have been documented in individuals with Fanconi anemia after undergoing bone marrow transplantation. Due to their heightened sensitivity to chemotherapeutic agents, individuals with Fanconi anemia often experience significant DNA impairment, leading

to poor cancer outcomes. Additionally, approximately 75% of individuals with FA present with congenital anomalies, which may include short stature and various cutaneous, skeletal, craniofacial, and genitourinary abnormalities [17, 18].

CONCLUSION

Fanconi Anaemia is one of a Congenital condition that mainly affects patients to aplasia, MDS (Myelodysplastic syndromes) etc. The patients need specialized follow up of multi-skilled clinical and biological competence. It also requires interprofessional team approach comparatively to other disease. Based on the degree of disease affected the number of health professionals are needed from different specialities. To maximize treatment, it is very important to understand the stepwise molecular & cellular mechanisms of Bone marrow failure, clonal evolution.

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