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Fanconi anemia

Abstract

Fanconi anemia (FA) is a rare, inherited disorder characterized by bone marrow failure, congenital malformations, and cancer predisposition. First described in 1927 by Guido Fanconi, FA primarily follows an autosomal recessive inheritance pattern, with mutations in DNA repair genes like FANCA, FANCC, and FANCG. It affects approximately 1 in 136,000 live births, with a slight male predominance. FA typically presents with pancytopenia, beginning with thrombocytopenia, followed by leukopenia and anemia. Physical manifestations span multiple systems, including endocrine, skeletal, ocular, and cardiovascular abnormalities. The risk of hematologic malignancies, particularly acute myeloid leukemia, is significantly elevated. Diagnosis involves cytogenetic testing for chromosomal breakage induced by agents like diepoxybutane or mitomycin C, alongside molecular genetic testing. Management includes supportive care with transfusions, hematopoietic stem cell transplantation (HSCT) as the sole curative option for marrow failure, and androgen therapy to stimulate hematopoiesis. Emerging treatments like gene therapy offer new hope. Despite medical advancements, FA carries a poor prognosis without timely intervention, with high mortality from marrow failure and malignancy. Lifelong monitoring and preventive strategies, such as HPV vaccination and avoiding environmental stressors, remain crucial to improving outcomes.

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Olivares-Schietekat Sebastián
Department of Nephrology and Mineral Metabolism, National Institute of Medical Sciences and Nutrition "Salvador Zubirán", México

Correspondence: Olivares-Schietekat Sebastián, Department of Nephrology and Mineral Metabolism, National Institute of Medical Sciences and Nutrition "Salvador Zubirán", México

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Introduction

Described for the first time in 1927 by the Swiss pediatrician Guido Fanconi, Fanconi anemia is the most common hereditary cause of spinal cord failure and aplastic anemia.[1] Being a disease with an autosomal recessive inheritance pattern, the pathology arises from mutations, duplications, splicing defects and/or deletions of up to 23 known FANC genes (90% in the FANCA, FANCC and FANCG genes),[2] belonging to the DNA repair pathway;[3] it is worth mentioning that the FANCB gene has an inheritance pattern linked to the X chromosome (2% of cases),[3] while the mutation of the FANCR gene (RAD51) is inherited with an autosomal pattern dominant (2 cases reported).[4,5]

FA proteins are responsible for repairing cross–links between DNA strands, therefore, in the event of a failure in said regulatory mechanism, a state of genomic instability is generated with chromosomal fragility, oxidative damage due to lower resistance to free radicals, susceptibility to cytotoxic drugs, hypersensitivity to ionizing and UV radiation, as well as a relevant predisposition to malignant neoplasms with a relative risk of up to 700, compared to the general population.[3]

Epidemiology

Epidemiologically, a prevalence of 1 case per 136,000 live births has been described and a carrier frequency of 1 in 180 people worldwide, with specific genetic predominance in the populations of South Africa and Spanish gypsies (FANCA gene), sub–Saharans (FANCG) and Ashkenazi Jews (FANCC) with prevalences of 1 in 40,000 births. These populations have a higher carrier frequency of 1 case per 83, 64–70, and 100people, respectively. In the United States it is estimated that approximately 31 children are born with the disease per year, and European data presents fewer rates with just 4–7 cases per million live births.[4] Fanconi anemia has as well a slight predilection by males (1.2:1).[3,6] The average age at the time of diagnosis is 7years, with a range from birth to over 50 years.[1]

Clinical Manifestations

Although a wide variety of signs and symptoms can occur, Fanconi anemia is mainly characterized by the presence of bone marrow failure, somatic malformations, and predisposition to malignant neoplasms.[2] Bone marrow failure manifests as pancytopenia, usually expressing thrombocytopenia prior to leukopenia and anemia. Symptoms of thrombocytopenia include episodes of epistaxis, petechiae, and unstoppable bleeding from a wound site, associated with elevated levels of fetal hemoglobin and macrocytosis; leukopenia increases the risk of infections; and finally, anemia causes general symptoms to manifest such as difficulty breathing, chest pain, dizziness and fatigue. Pancytopenia can be classified as mild, moderate or severe depending on the levels of depletion in the cell count of the three bone marrow lines.[3,6] Physical manifestations occur in 75% of affected patients and are shown below in Table 1.

Table 1 Physical manifestations of patients with Fanconi anemia.[3,6,7]

System	Physical Alterations
Endocrine (73%)	Short stature, low birth weight, hypothyroidism, midline brain abnormalities, primary hypogonadism, glucose/insulin metabolism disorders, dyslipidemia, metabolic syndrome, osteopenia/osteoporosis.
Skin (40%)	Hypopigmentation or hyperpigmentation, café–au–lait spots, pallor, petechiae, bruising.
Skeletal (35%)	Spina bifida, scoliosis, kyphosis, vertebral fusion, sacral agenesis or hypoplasia, absent clavicle, Sprengel deformity, Klippel–Feil anomaly, rib abnormalities, absence of the first metacarpal, ulnar or radial hypoplasia/aplasia, brachydactyly, arachnodactyly, clinodactyly, polydactyly, Perthes disease, hip developmental dysplasia, femoral osteoma, lower limb asymmetry, clubfoot.
Muscular (35%)	Thenar hypoplasia, unilateral/bilateral thumb hypoplasia, floating thumb, bifid thumb, digitized or displaced thumb, supernumerary thumb, absent thumb.
Genital (25% in males and 2% in females)	Hypogenitalism, infertility, gonadal dysgenesis. Micropenis, hypospadias, chordee, penoscrotal fusion, phimosis, cryptorchidism, atrophic or absent testes, hypo/azoospermia. Dysplastic or absent ovaries, bicornuate uterus, uterine hypoplasia/aplasia, vaginal atresia/hypoplasia, labial fusion/hypoplasia.

Table 1 Continued...

System	Physical Alterations
Ocular (20%)	Microphthalmia, microcornea, hypotelorism or hypertelorism, small and almond–shaped palpebral fissures, proptosis, eyelid ptosis, epicanthal folds, strabismus, astigmatism, cataracts, ocular epiphora, optic nerve hypoplasia.
Urinary (20%)	Ectopic kidney, horseshoe kidney, rotated kidney, renal dysplasia, renal hypoplasia or agenesis, hydronephrosis, hydroureter, ureteral reflux or stenosis.
Auditory (10%)	Prominent, low–set, and/or rotated auricles, microtia, small or absent auditory canals, absent tympanic membrane, ossicular sclerosis, hearing loss.

It is worth mentioning that there is a clear genotype–phenotype relationship in which the mutations present in the FANC genes determine the predisposition to certain physical manifestations in the individual; It is estimated that 80% of people with mutations in the FANCB, D1, D2, I, J and N genes will present at least one somatic malformation.[1]

The main malignant neoplasms that affected individuals present are: Acute myeloid leukemia at 15 to 35years of age, myelodysplastic syndrome associated with monosomy 7 and 7q deletion, squamous cell carcinomas of the head, neck, upper esophagus and anogenital region with a presentation between 20 to 40years of age, Wilms tumor, neuroblastoma or medulloblastoma in patients with mutations in FANCD1, as well as liver tumors in patients on androgen treatment.[6,7]

In addition to clinical suspicion, a diagnostic study should be suspected and requested in patients who present macrocytosis, elevated fetal hemoglobin or serum erythropoietin, a family history of Fanconi anemia or the presence of the disease in siblings, or unusual sensitivity to chemotherapy or radiotherapy.[7]

Diagnosis

When requesting a blood count, it will reveal a decrease in platelet and absolute neutrophil counts, as well as a decrease in hemoglobin levels and an increase in ESR. The aspirate and bone marrow are characterized by hypoplasia and hypocellularity with characteristics of fatty replacement of aplastic anemia; islands of hyperplastic erythroblasts or erythroid dysplasia can also be observed.[3] The diagnosis is confirmed by a cytogenetic study of chromosome breakage, centric and acentric fragments, or radial figures of a culture of lymphocytes (or skin fibroblasts if mosaicism is suspected if the first test is normal or inconclusive) exposed to diepoxybutane and/or mitomycin C. Another alternative for diagnostic confirmation is the identification of the biallelic pathogenic variants previously described through studies molecular.[6]

A differential diagnosis should be established with any acquired aplastic anemia, other hereditary bone marrow failure syndrome (congenital dyskeratosis, reticular dysgenesis, Diamond–Blackf and anemia, Schwachman–Diamond syndrome, amegakaryocytic thrombocytopenia), Denovo myelodysplastic syndrome, suspected pancytopenia drug– induced or infection–associated, paroxysmal nocturnal hemoglobinuria, neurofibromatosis type 1, thrombocytopenia with radial aplasia, VACTERL association, Baller–Gerold syndrome, Dubowitz syndrome, Holt Oram syndrome, Townes–Brocks syndrome, or other rare chromosome breakage syndromes (Bloom syndromes, LIG4, Nijmegen break, Seckel break, of Warsaw, Robert, ataxia–telangiectasia, NHEJ deficiency 1).[3,6-8]

Treatment and Management

The treatment of complications is multifaceted and has various approach mechanisms. Supportive treatment consists of blood, platelet, and packed red blood cell transfusions from unrelated donors to prevent graft–versus–host disease; For lymphopenia, it is recommended to use granulocyte colony–stimulating factor at a minimum dose and frequency if the absolute neutrophil count is <200/mm. Hematopoietic stem cell transplantation (response in 50–75%) is indicated in patients with severe aplastic anemia, and at risk of developing acute myeloid leukemia, myelodysplastic syndrome; However, it does not reduce the high susceptibility of other types of neoplasms and tumors.[3,7]

Patients require specific regimens for bone marrow transplantation, so the use of fludarabine is recommended as an alternative to radiation. This drug has been shown to reduce the incidence of graft–versus–host disease, and allows a one–year survival rate of 80%.[6]

Likewise, the use of androgens is used to stimulate the proliferation of hematopoietic stem cells, or in case hemoglobin is below 8 g/dL or platelets below 30,000/mm^3. The drugs oxymetholone (2–5mg/kg/day), danazol (minimum effective dose), stanozolol or oxandrolone are used with the warning that they can cause cholestasis, peliosis hepatis and liver tumors.[3,6]

Patients may require surgical treatment to correct congenital structural deformities, or if possible, for possible malignant neoplasms that may arise, given the patients' hypersensitivity to chemotherapy and radiotherapy.[3]

The latest advances in the treatment of Fanconi anemia include gene therapy of replacement of the affected gene with a normal gene with gamma–retroviral, lentiviral or foamy viral vectors; given that they have the advantage of being an alternative to allogeneic transplant and presenting low toxicity compared to chemotherapy in current regimens. Likewise, non–viral vectors and pseudo typed lentiviral vectors have emerged that are specifically directed at CD34+ cells. Finally, advances are also being made in gene editing through specific nucleases that increase the efficiency of homologous recombination of specific regions of the genome or reprogram other cells such as fibroblasts or keratinocytes to generate induced pluripotent stem cells that serve as hematopoietic precursors.[9]

Prognosis and Follow–up

The prognosis is unfavorable, with a life expectancy of less than 10 years due to early mortality due to severe aplastic anemia if not diagnosed, and a 33% risk of developing acute myeloid leukemia or myelodysplastic syndrome at the age of 40years.[3,7] After a hematopoietic transplant, 3–year survival is 85%.[8]

Therefore, early prevention and surveillance measures must be adopted, including the implementation of the HPV vaccine at the age of 9, avoiding blood transfusions from family members, avoiding tobacco, alcohol and unprotected sexual practices, and minimize radiological studies that do not have an absolute medical indication.[6]

Regarding patient follow–up, multiple considerations must be taken into account, such as adopting treatment regimens without radiotherapy, depleting T cells from the bone marrow donor graft, performing a complete annual multidisciplinary evaluation, performing a blood count every 3months or in a shorter time if required, as well as a bone marrow aspirate every year that evaluates morphology, cellularity, FISH and cytogenetics, evaluate liver function every 3 to 6months and perform a liver ultrasound study every 6 to 6months,

12months if the patient receives androgen treatment, schedule annual gynecological examinations from the age of 13years and Pap tests at the age of 18 years or at the beginning of sexual activity, examine with nasopharyngoscopy every 6months, as well as evaluate the mouth , head and neck from 9–10years of age, examine the patient every 2–3months if they have a history of malignant lesions, and perform a screening every 6months in search of neuroblastomas, brain or kidney tumors. Pregnant patients should be classified as having a high–risk pregnancy and need to be evaluated by a highly specialized gynecologist–obstetrician in conjunction with a hematologist.[6]

Conclusion

Fanconi anemia is a rare but severe genetic disorder characterized by bone marrow failure, congenital abnormalities, and a high predisposition to malignancies. Advances in diagnostic techniques, including molecular genetic testing, have improved early detection, while hematopoietic stem cell transplantation remains the only curative treatment for bone marrow failure. Emerging therapies, such as gene therapy and targeted molecular approaches, hold promise for improving patient outcomes. However, due to the high risk of complications, lifelong surveillance and preventative measures are essential. Continued research and awareness are crucial in enhancing both the quality of life and life expectancy of individuals affected by this condition.

Acknowledgment

None.

Conflicts of interest

The authors declare there is no conflict of interest.

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