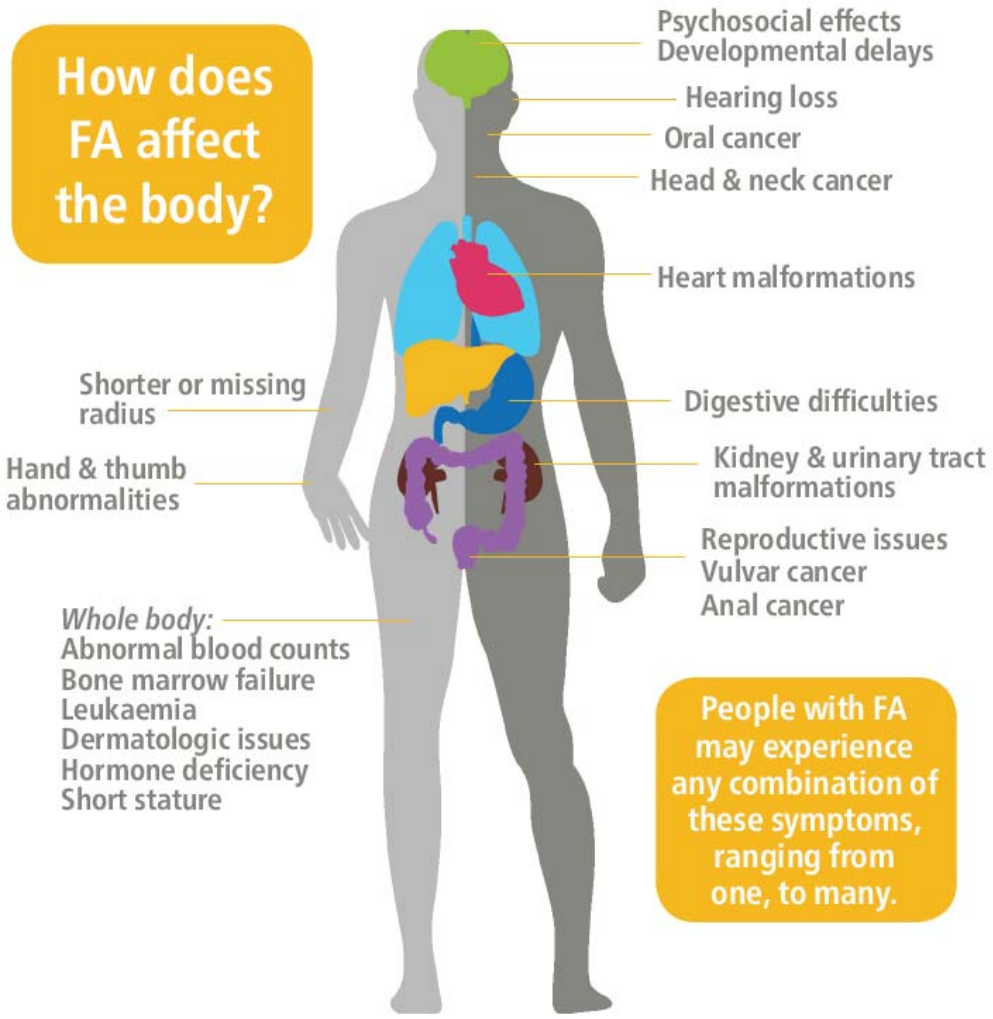
About Fanconi Anaemia for Non-FA specialist Medical Professionals

Summary

Fanconi anaemia (FA) is a genetic DNA repair disorder that may lead to bone marrow failure, leukaemia, and/or solid tumours (cancer). It is caused by one of at least 23 genes. FA can affect all systems of the body. It is a complex and chronic disease that is psychologically demanding.



Epidemiology

Recent determination of the carrier frequency gave an estimate of more than 1/200, with an expected prevalence at birth of at least 1/160,000. In certain populations, the carrier frequency is much higher, due to founder mutations. Until now, more than 2,000 cases have been reported in the literature.

Clinical description

In 2/3 of patients, the first signs of FA are congenital malformations that may involve the skeleton, skin, uro-genital, cardio-pulmonary, gastrointestinal and central nervous systems. Limb anomalies are unilateral or bilateral, the latter being frequently asymmetrical. Minor anomalies can also be present such as low height and weight, microcephaly and/or microphthalmia. Skin pigmentation abnormalities and hypoplastic thenar eminence are frequent. Almost 20% of patients have ear malformations with or without hearing loss. Congenital malformations may vary in a family. When congenital malformations are not prominent, diagnosis may be delayed until the onset of bone marrow failure (BMF), which occurs at a median age of 7 years. Haematologic abnormalities may occur at a younger age and, more rarely, in adults, with 90% of patients developing BMF by 40 years of age. Patients may develop acute myeloid leukaemia, often preceded by myelodysplastic syndrome. Patients are also highly predisposed to solid tumours, of the head and neck or anogenital regions. Short stature is often secondary to hormonal deficiencies. Fertility is almost totally impaired in males, and is highly disturbed in half of females. Pregnancy is often complicated.

Etiology

FA is due to mutations in genes involved in DNA repair and genomic stability. To date (2019) 23 genes representing 23 complementation groups have been identified.

Diagnostic methods

Given the high heterogeneity in genetic causation and clinical phenotype, and the pathogenic mechanism of FA, diagnosis relies on the evaluation of chromosomal breakage induced by diepoxybutane (DEB) or mitomycin C (MMC).

Differential diagnosis

FA clinical manifestations overlap with many malformation syndromes (Dubowitz, Seckel, Holt-Oram, Baller-Gerold, thrombocytopenia-absent radius, Nijmegen breakage syndromes, VACTERL association, dyskeratosis congenita; see these terms) and diagnosis of FA is often delayed until a patient develops BMF or malignancies. FA should be considered in the differential diagnosis of all young patients with BMF of unknown etiology. Other cancer predisposition syndromes (Bloom, Rothmund-Thomson or Werner syndromes; see these terms) or syndromes with pancytopenia (Diamond-Blackfan anaemia, immune pancytopenia, Pearson or Shwachman-Diamond syndromes; see these terms) should be considered.

Antenatal diagnosis

Prenatal diagnosis is feasible with a DEB-induced chromosomal breakage assay or by molecular study when the mutation is known.

Genetic counselling

FA is usually an autosomal recessive disorder but X-linked transmission may occur.

Management and treatment

Supportive care includes transfusions of packed red blood cells (RBC) or leucodepleted platelets. The only curative treatment for haematologic manifestations is haematopoietic stem cell transplantation (HSCT). However, this approach tends to increase the solid tumour risk, which must be specially monitored. Symptomatic treatment includes oral androgen administration, which improves blood counts in some patients, in particular RBC. Administration of haematopoietic growth factor could be considered after bone marrow aspirate and biopsy, which should be regularly performed during the treatment. When malignancies develop, treatment is complicated by the sensitivity to radiation and chemotherapy of FA patients.

Prognosis

BMF and malignancies lead to a poor prognosis with a reduced life expectancy, which has been improved by HSCT and androgen treatment

Sources

Page 1: Fanconi Anemia Research Fund, Oregon USA. Last update: ***April 2019.***

Pages 2-4: Orphanet (www.orpha.net)

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