Fanconi anaemia

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Identity

Alias
Fanconi pancytopenia

Note
Fanconi anaemia is a chromosome instability syndrome with progressive bone marrow failure and an increased risk of cancers.

Inheritance
Autosomal recessive; frequency is about 2.5/10^5 newborns.

Clinics

Phenotype and clinics
Growth retardation (70% of cases).
Skin abnormalities: hyperpigmentation and/or café au lait spots in 80%.
Skeletal malformations (60%), particularly radius axis defects (absent or hypoplastic thumb or radius...).
No immune deficiency (in contrast with most other chromosome instability syndromes).
Progressive bone marrow failure; mean age of onset of anemia: 8 yrs; diagnosis made before onset of haematologic manifestations in only 30%.
Other: renal anomalies, hypogonadism, mental impairment, heart defects, and perhaps diabetes mellitus, also occur in 10 to 30% of cases.

Neoplastic risk
Myelodysplasia (MDS) and acute non lypchocytic leukaemia (ANLL): 15% of cases; i.e. a 15000 fold increased risk of MDS and ANLL has been evaluated in FA, and it has been assumed that it is reasonable to regard the Fanconi anemia genotype as "preleukemia";
mean age at diagnosis: 13-15 yrs
Hepatocarcinoma (androgen-therapy induced) in 10%;
mean age at diagnosis: 16 yrs.
Other cancers in 2-5%: in particular squamous cell carcinoma.

Treatment
Androgens and steroids to improve haematopoietic functions; bone marrow transplantation prevents from terminal pancytopenia, and from ANLL as well.

Prognosis
Mean age at death: 16 years; most patients die from narrow aplasia (haemorrhage, sepsis), and others from malignancies; MDS and ANLL in FA bear a very poor prognosis (median survival of about 6 mths); survival is also poor in the case of a squamous cell carcinoma.

It has recently been shown that significant phenotypic differences were found between the various complementation groups (see below). In FA group A, patients homozygous for null mutations had an earlier onset of anemia and a higher incidence of leukemia than those with mutations producing an altered protein. FA group G patients had more severe cytopenia and a higher incidence of leukemia. FA group C patients had less somatic abnormalities, which, in reverse, were more frequent in the rare groups FA-D, FA-E, and FA-F. FA group G patients patients and patients homozygous for null mutations in FANCA are high-risk groups with a poor hematologic outcome and should be considered as candidates both for
frequent monitoring and early therapeutic intervention. There may also be a certain degree of clinical heterogeneity according to the degree of mosaicism. Therefore, clinical manifestations may be variable within a given family, according to the stage of embryonic development at which the somatic reverse mutation occurred.

**Cytogenetics**

***Inborn conditions***
Spontaneous chromatid/chromosome breaks, triradials, quadriradials.
Hypersensitivity to the clastogenic effect of DNA cross-linking agents (increased rate of breaks and radial figures); diepoxybutane, mitomycin C, or mechlorethamine hydrochlorid are used for diagnosis.

**Cytogenetics of cancer**
Various clonal anomalies are found in MDS or ANLL in Fanconi anaemia patients, such as the classical -5/del(5q), and -7/del(7q), found in 10% of cases; telomeres appear to be non randomly involved in FA's clonal anomalies.

**Other findings**

***Note***
Slowing of the cell cycle (G2/M transition, with accumulating of cells in G2).
Impaired oxygen metabolism.
Defective P53 induction.

**Genes involved and proteins**

***Note***
The most prevalent complementation groups are: group A (65-70% of cases), groups C and G (10-15% each)
Rare complementation groups are groups B, D, E, and F (Six genes have been discovered, corresponding to the frequent phenotypes: FANCA in 16q24, FANCC in 9q22, and FANCG in 9p13, and to the rarer phenotypes FANCD2 in 3p25. FANCE in 6p21, and FANCF in 11p15. The genes FANCB and FANCD1 have yet to be uncovered.

**To be noted**

***Note***
Clinical diagnosis may, in certain cases, be very difficult; cytogenetic ascertainment is then particularly useful; however, cytogenetic diagnosis may also, at times, be very uncertain; this is a great problem when bone marrow engraftment has been decided in a pancytopenic patient: if this patient has FA, bone marrow conditioning must be very mild, as FA cells are very clastogen sensitive. The recent discovery of genes involved in the disease should improve diagnostic ascertainment.

FA patients (i.e. patients with defective alleles) may have, in a percentage of cells, a somatic reversion (by revert mutation towards wild-type gene); such a phenomenon is also known in Bloom syndrome, another chromosome instability syndrome.

**References**


Diatloff-Zito C, DUCHAUD E, VIEGAS-Pequignot E, Fraser D, Moustacchi E. Identification and chromosomal localization of a DNA fragment implicated in the partial correction of the Fanconi anemia group D cellular defect. Mutat Res. 1994 May 1;307(1):33-42


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