E9. FANCONI ANEMIA. DIAGNOSIS AND MANAGEMENT GUIDELINES.

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Until now, at least 13 types of Fanconi anemia (FA) have been described, each of them characterised by a complex molecular pathology. Determining the genotypes of the patients and mutational analysis are advisable in every case as they play an important role in choosing therapy. FA can be described as a multiple stage affliction. The hematological manifestations do not represent the main symptoms of a patient with FA and are not the only clinical manifestations either. The genetic instability of the patient with FA is caused by the exposure to ionising radiation, carcinogenic agents of environmental nature and chemotherapy. Thus, the exposure to X-rays is an undesirable risk.

Cerebral tumours (before the age of five), Wilms tumour (highest incidence at the age of four) and other renal cancers (at patients with BRCA2 idiotype multiple studies are in progress) can develop.

As stem cell transplant from related donors or skin grafts "in mismatch" are nowadays a challenge, this option becomes valid for an increasing number of patients with FA. Because the prevalence of squamous cancers especially of the integument, head, neck and also genitals is high, the evaluation of adult patients before the selection of therapy is essential. After the primary exam, an endocrinologic and gastrointestinal evaluation is required. The patient and his family must be psychologically observed due to the possible traumata.

Tests for diagnosis

The suspicion of FA requires the hospitalisation and exploration of the patient in specialised clinics with experience in the diagnosis and treatment of this illness.

Classification of clinical manifestations of FA	
Hematological	cytopenia (can precede the installment of bone marrow failure), increased risk of developing myelodysplastic syndromes and AML (beginning from the age of 13, the risk of AML increases 800 times in patients with FA)
Dermatological	hyperpigmentation, „café au lait" skin, hypopig mented areas, squamous cancers with different sites of localisation (skin, cervix, vagina, vulva, anal canal)
Gastrointestinal and hepatic	about 7% of the patients with FA have anomalies of the gastrointestinal tract (ozena, nausea, vomitus, abdominal pain). Esophageal, duodenal or jejunal atresias, eso -tracheal fistulas, anus imperforatum can exist. Hepatic tumours may appear in the absence of alcohol consumption or of an acute viral hepatitis in the past
Cardio-pulmonary	closely associated with cardio-pulmonary malformations
Locomotory	absent/bifid/vestigial/triphalangeal fingers, syndactyly, digital hypoplasia; absent or hypoplastic radius, dysplastic ulna, hypoplasia of the hypothenar eminence or the absence of the 1 st metacarpal; micrognathia, microcephaly, triangular facies. The patient may present spina bifida, scoliosis. Sprengel or Klippel -Feil syndromes may be associated with the locomotory manifestations
Ocular	microphtalmia, strabismus, epicanthus, cataract, astigmatism
Renal	Ectopic kidneys, renal hypoplasia/dysplasia/atresia, hydronephrosis, hydroureter
Endocrinologic	hypothyroidism, late puberty, diabetes mellitus, osteopenia/osteoporosis
ORL	atresia of the auricle of the ear, deafness or hypoacusia
Gynecologic	hypogenitalism, ectopic testes, hypospadias, micropenis in men; hypogenitalism, bicornuate uterus, infertility, abnormal menstruation in women

The exploration begins with cytogenetic tests which reflect the fragility of chromosomes: DEB (Diepoxybutane) and MMC (Mitomycin) tests conducted on lymphocytes from peripheral blood. All children suspected of FA, once hospitalised, will be evaluated: familial history, consanguinity, FA AHC, physical abnormalities, neoplasms, medullary aspiration and biopsy, imaging techniques (ultrasonography) for patients with renal dysplasias and hydronephrosis. After the peripheral blood exam has been conducted, medication should be administered. The hepatic (bilirubin, ASAT, ALAT) and renal (serum electrolytes, creatinine) functions will be evaluated. The urologic exam is useful in the diagnosis of genitourinary reflux, urinary infection and genitourinary malformations. Then, endocrinologic evaluation should target the: thyroid function, glycemia, OGTT, lipid profile, osteo-medullary density, discovery of osseous abnormalities. The ophthalmologic exam is mandatory.

The risk of cancer will be identified to both pacient and relatives. Through genomic analysis, FANCD1/BRCA2, D2, I, M, N will be identified. Mutational analysis is required to classify the patient into one of the five genomic groups. The most advanced genetic and prenatal tests will be conducted, but only in specialised centres. The severity of FA is determined by the specific gene FANC. The patients with FANCA do not present homozygotic mutations which account for the sinthesis of proteins able of inducing anemia or a high susceptibility for the development of AML. The type of homomorphic mutation FANCA produces proteins with an abnormal structure. FANCC IV S4+4 A>T, common in Ashkenazi Jews, is associated with severe and aplastic anemia. VACTERL-H is frequent and is associated with vertebral/anal malformations, eso-tracheal fistulas and renal abnormalities. At Japanese patients with FA, FANCC IV S4+ A>T is prevalent, but is linked with a better phenotype than the one of Ashkenazi Jews. The FANCD1/BRCA2 and FANCN/PALB2 mutations are associated with an increased predisposition of AML and an abnormal physical phenotype. The abnormalities of the VACTERL-H cluster are correlated with the biallelic mutations FANCD1/BRCA2 type. The FANCD 2 and FANCI mutations are associated with severe

abnormalities and FANCI1 with the development of an early anemic syndrome.

The majority of patients with FA develop aplastic anemia, but the age of development is variable. In case of AML or SMD development, cytogenetic abnormalities should be detected. The HLA typing will be conducted to both patient and family to discover possible donors. The transfusional treatment will be cautiously administered. The patient who has undergone multiple transfusions is at high risk of secondary hemochromatosis. Iron can accumulate in the liver, heart or endocrine organs. In time, hemochromatotic cirrhosis, cardiomyopathy, endocrine disorders can evolve. After the transplant, iron metabolism will be supervised and iron chelators will be used only after one year after the transplant. Sometimes, phlebotomies will be necessary. No drug will be given to the patient without notifying the therapist. Radiological exams will be avoided or cautiously performed. All abnormalities of the skeleto-muscular system will be detected and an orthopedic exam will be methodically performed. All finger abnormalities impose orthopedic interventions. The psychologic support of the patient will not be neglected.

Ocular and ORL malformations will be registered and ophthalmologic and ORL exams will be conducted starting with the age of four months as surgical procedures meant to correct defects are recommended. The patient will be monitored by a handicap commission, verbal therapy being required. If the patient has received ototoxic medication, antibiotics IV, iron chelators, CT, after the transplant audiograms are necessary. Gastroenterologic control and treatment are also mandatory. Hepatic complicantions are sometimes caused by the treatment with androgens. Every six months, ASAT, ALAT and ultrasonographic exams should be repeated. Due to the risk of developing squamous cancers of the genital tract (cervix, vagina, vulva, anal canal), gynecologic exams in patients over 13 are advisable. External genital organs will be inspected. After 18, cervical cytologic exams (Papanicolau test) will be conducted. Oral contraceptives will be administered. Colposcopy is required if lesions of the cervix or cytologic abnormalities are present. Since the age of nine, the HPV test is obligatory to prevent neoplasms. Abnormalities of the genital tract are more frequent in patients with renal malformations. Breast cancer is also frequent in women with FA who should be monitored since the age of 20 and in women over 25 "screening" mamographies are to be made. Each woman who has undergone a transplant will be monitored in case of pregnancy. Administration of androgens is forbidden in this case. Women with FA can have risky pregnancies, premature menopause, major cardiovascular risk, squamous cancer risk of the head and neck (HNSCC). Each patient with HNSCC will be investigated: hematologic abnormalities (anemia, monocitosis, and thrombocitopenia), finger abnormalities; in case of cancer, an unusual response to CT will be investigated. ORL exam will be conducted since the first year of life (nasopharynx, oropharyns, and larynx). Oral hygiene will be cautiously supervised and alcohol consumption and smoking will be interdicted. After TMO, a major risk of infections and bacteremias exists.

Each cutaneous lesion will be supervised (pigmented warts especially, those with with mutations of the FANCD1/BRCA2 having the highest risk of developing a cutaneous squamous cancer). The risk of developing medulloblastoma is higher in these patients and annual cerebral MRI ought to be performed. Patients with FA may develop esophageal and genital neoplasms at about 20 years.

In conclusion, the presence of FA should be suspected in the following cases: the existence of one or more cases of FA in the patient's family, abnormalities of the skeleto-muscular system (abnormal/dysplastic radius or ulna, abnormal fingers, renal abnormalities, microphtalmia, microcephalia, microcephaly), development of aplastic anemia, „café au lait" skin, eso-tracheal fistulas, anus imperforatum, primary AML or myelodysplastic syndrome diagnosis, abnormal sensitivity to CT. FA can be suspected if anal/vulvar neoplasms develop under 40 years. The physician can think of this diagnosis in case of cytopenia, unexplainable macrocytosis (serum B12 vitamin, folates – normal levels), hepatic tumours, ovarian insufficiency before the age of 30, infertility, cerebral tumours before the age of five and Wilms tumours in children under four years.

Cytogenetic exam (monosomy 7 syndrome & 1,3,4,7 pairs of chromosomes are observed) will be conducted. Frequently, the 3q26q29 endoreduplication (trisomy or partial tetrasomy) appears. Monosomy 7 syndrome is also prevalent (the 3q clone) and one third of the affected patients develop myelodysplastic or primary AML. All cases in which chromosome 3 is amplified will be investigated (the chromosomal material of the G band will be used for genomic exams). Amplifications of the 3q chromosome will be confirmed by FISH or SKY technique. Comparative genomic hybridisation will also be performed. As FA patients with abnormalities of the 3q clone present a higher risk of developing AML, they will be cautiously evaluated as they can undergo marrow transplants.

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