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Case Report

Late Diagnosed Fanconi Anemia and Practical Consequences

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• Fanconi; Malformations; Cerebral microangiopathy; Small size; Pancytopenia

Abstract

8-year-old girl admitted for management of left hemi paresis. The CT scan supplemented with MRI angiography revealed ischemic lesions related to cerebral microangiopathy. The association of limb and kidney malformations, as well as the small size and pancytopenia had led us to anemia of fanconi.

ABBREVIATIONS

FA: Fanconi Anemia; B2GP1: Anticorps anti-bêta 2 glycoprotéine 1; FAN: Factor antinuclear; MCI: Mild Cognitive Impairment; AD: Alzheimer's disease; SSRIs: Selective Serotonin; RI: Reuptake Inhibitors

INTRODUCTION

Fanconi anemia (FA) is a rare genetic disease, it is transmitted through both autosomal and X-linked recessive modes. It is characterized by congenital malformations, progressive marrow failure and predisposition to acute myelogenous leukemia (AML) and other malignancies.

The prevalence of FA is 1 to 5 cases per 1 million persons and the heterozygous carrier frequency is about 1 case per 300 persons. The ratio between sexes is about equal. FA is diagnosed at children aged between 5 and 15 years.

Chromosomal instability, especially on exposure to alkylating agents (mitomycin C or diepoxybutane) are useful for a diagnostic test. Hypersensitivity to cross linking agents increase chromosome breakage and provides the basis for a diagnostic test. FA can be caused by mutations in at least 13 different genes. Bone marrow transplantation is the only treatment that definitively restores hematopoiesisat patients.

CASE PRESENTATION

We report a case of an 8year-old girl, admitted in the pediatrics hospital of Belfort for management of left hemi paresis. From physiological and pathological history we noted: notion of consanguinity 3rd degree, natural birth, birth weight 2400g, stunting delay since early age and two transfusions for acute anemia.

Clinical examination indicated a body mass index of 17.70 (weight 17 kg, height 98 cm), short stature, a microcephaly, triangular looking face, and coffee-and-milk spots with melanoderma at the neck and trunk with absent right hypoplastic thumb and radii. Left motor deficit, with aphasia, rhythmic heart sounds, pulse = 80/min, blood pressure = 94/50 mmHg, no breath or added noise.

Laboratory investigations related: pancytopenia (Leucocytes= 2450/mm^3, Hemoglobin = 7.31g/dl, platelets= 200/mm^3), moderate macrocytosis, hypochromia and severe thrombocytopenia. Hemoglobin electrophoresis with high HbF levels, very high erythropoietin serum level. Renal impairment stage II with creatinine clearance: 25 ml / min / 1.73.

Bone marrow puncture was performed to confirm the diagnosis, which revealed a bone with low cellularity, apparently without morphological modifications, confirmed by the biopsy which revealed a bone marrow with low cellularity.

Chromosome breakage studies using mytomicine B could not be practiced, but the diagnosis remains obvious for our patient.

Viral serologies: HBS, HCV, HIV, Syphilis, Widal, Wright were all negative.

Cerebral CT scan revealed multiple sub facial bilateral multifocal ischemic lesions confluent on the left. Cerebral MRI angiography had objectified cerebral microangiopathy cerebral ischemic left fronto-parietal ischemic on occlusion of the ipsilateral sylvian artery.

Ultrasonography visualized Small ectopic echogenic kidney kidneys, differences of chronic nephropathy, no dilatation of intrarenal cavities and ureteric basins Cysto-urethrogram during urination (CUM) concludes Vesicoureteral reflux grade V.

Uro-MRI: ectopic maltly kidneys in pelvic position fused together by their superior poles, each kidney has its own excretory

system. The determination of the proteins of coagulation protein C,S, Antithrombine, Activated protein C resistance with or without factor V Leiden mutation was normal; balance of autoimmunity in particular, , FAN , anti DNA-natif ; Ac anti Bêta 2 GP1 IgG , anti-cardiolipine IgGwqs normal.

Treatment of the renal failure consists as conservative measures such as weight reduction, exercise, and dietary salt reduction, and of treatment of renal osteodystrophy with vitamin D and calcium substitution.

endoscopic treatment of the urétero reflux appealed to deflux. Unfortunately the bone marrow transplant was rejected in this patient because of the associated malformations and kidney damage. Our patient was put in androgens type Nilevar with raison of 10mg / kg / d.

DISCUSSION

Fanconi's Anaemia (FA) is an autosomal recessive disorder, characterised by progressive pancytopaenia, associated congenital abnormalities and a high risk of developing leukaemia. It was first described by Guido Fanconi, a Swiss paediatrician, in 1927, who documented a form of a plastic anemia present in 3 brothers with short stature, hypogonadism and abnormal skin pigmentation [1].Since then, over 900 cases have been reported [2] enabling the disease to be clearly defined.

Two large international studies characterized the clinical phenotype of individuals with different mutations in the FANCA gene. The initial study carried out in 2000 found that FANCA individuals with homozygous null mutations had a higher frequency of somatic anomalies than individuals with FANCC mutations, but a similar frequency to those with FANCG mutations. FANCA individuals were also at increased risk for severe haematological disease. A number of the patients in this study were of Afrikaner ancestry and had at least one null del1231 mutation [3]. Until recently, there were thought to be at least eight FA complementation groups determined by somatic cell hybridisation, FA-A, B, C, D1, D2, E, F, G. Six of the FA genes (FANCA, C,D2, E, F, G) have been cloned and it now appears that FANCD1and possibly also FANCB are in fact BRCA2 [4].

In 2011, research into the functional role and clinical impact of FANCA mutations challenged the earlier findings. The authors concluded that mutation type had little prognostic value in FANCA patients and that other factors, including genetic back ground, ethnicity and environmental exposure were more importantin determining the clinical outcome [5].

FA is the commonest type of inherited bone marrow failure syndrome and the incidences of aplastic anaemia, myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML) are all greatly increased in homozygotes [5,6]. At birth, the blood count is usually normal and macrocytosis is often the first detected abnormality followed by thrombocytopenia and neutropenia [7].

Pancytopenia typically presents between the ages of 5 and 10 years, the median age of onset being 7 years [8].

The treatment of choice is bone marrow transplantation, which may be curative. Future therapies may well include gene therapy and as the corrected FA cells are likely to have a selective advantage over the defective3ones, this will eliminate the need for bone marrow transplantation [9].

Skeletal abnormalities are the most common (70%) and include radial ray defects (hypoplasia of the thumb and or radius), rib and vertebral defects and congenital hipdislocation. Small or absent thumbs are considered a hall-mark of the syndrome. These children are generally of short stature, Renal abnormalities are present in approximately one third of patients and include unilateral renal aplasia, renal hypoplasia, horseshoe kidneys, or double 24 ureters. In males there is a high incidence of genital abnormalities such as hypogenitalia, undescended testes, and hypospadias, and infertility is usual, although there have been reports of males with FA fathering children.

We think that the only observation, after that reported by Radheshyam Purkai et al.[9], is the occurrence of a hypertensive encephalopathy in a patient with fanconi anemia and renal artery stenosis; and that reported by Hilal MOCAN et al.[10], on acute renal failure revealing anemia of fanconi in a young adult, with regard to reflux vesico-ureteral; our review of literature has found a publication of Haddad et al.[11], which describes reflux as associated with several other urinary malformations.

Unfortunately bone marrow transplantation only curative treatment for our patient was rescued because of kidney failure and associated brain malformations. This has complicated the management in this child despite its placing under nilevar, we fear in the future a non response see a mandatory use of transfusions, erythropoietin and especially the deterioration of its renal failure which will indicate in this case the kidney transplant.

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