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Hereditary Hemochromatosis: About A Moroccan Family

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Abstract | **Case Report**

Hereditary hemochromatosis is a genetic disease that causes iron overload and its precipitation in different organs. In the African population, it is an extremely rare disease. To our knowledge, in the literature no case of North African family has been reported, so we report our experience with a Moroccan family with hemochromatosis.
Keywords: Hereditary hemochromatosis, ferric overload, cancer risk.

INTRODUCTION

Hereditary hemochromatosis (HHC) is an autosomal recessive disease witch can affect a wide variety of organs and lead to potentially life-threatening. In addition to excessive iron consumption, mutations of the HFE gene in patients with HHC are associated with an increased risk of cancer. Through this work, we report our experience with the first North African family with hemochromatosis and highlighting the disease and the associated cancer risk.

Case Report

Case 1

B.H, 48 years old. Admitted for hepatic colic. She is diabetic type II since the age of 36 years under metformin. As family history: a consanguinity of the parents of 2nd degree. 2 sisters and one brother with hemochromatosis. Physical exam shows: a portal hypertension syndrome on probable liver cirrhosis. Abdominal ultrasound showed heterogeneous hepatomegaly, with two masses at segment IV and III . Hepatic MRI showed multiple secondary parenchymal lesions, the largest one occurred in segment III and IV-V on a hemochromatosis liver. These lesions are responsible for a mass effect on the portal branches that are compressed but remain permeable. The thoracic and pelvic scans did not show any other lesion. Upper Fibroscopy objective oesophageal varices grade I with Hypertensive Gastropathy. Colonoscopy revealed a right colon cancer, stenosing stopping progression beyond. The histology shows a moderate differentiated infiltrating adenocarcinoma. Biology showed hepatocellular insufficiency (TP at 49% albumin at 29.31), cholestasis (PAL = 335 GGT = 297 BT = 12), Ferritinemia at 12312, transferrin saturation factor (TSF) at 50% (2 occasions). Tumor markers: ca19-9> 24000 IU / ml, ACE = 799, 42ng / ml, protein electrophoresis shows an inflammatory syndrome with a significant hypo albuminemia HVC- HVB serology were negative. The genetic study showed an H63D mutation of the HFE gene in the heterozygous state. The ECG and echocardiography was without abnormalities Thus the diagnosis of hemochromatosis with a metastatic adenocarcinoma and the patient was a candidate for palliative chemotherapy. The patient is dead because of major alteration of the general state.

Case 2

B.M, 41 years old. Sister of the first patient. Diabetic type II under metformin, penicillin Allergic, primary amenorrhea undergoing replacement therapy with intermittent hepatic colic associated sometimes with mechanical arthralgia in a good health state . The clinical examination is without particularity. Hepatic MRI showed a hepato siderosis. The ferritinemia is at 2014 mg / l, serum iron at 2, 53mg / l, transferrin saturation factor at 82%. Protein electrophoresis showed an inflammatory syndrome associated with a significant hypo albuminemia, HVC-HVB serology negative. Liver biopsy showed hemochromatosis with massive steatosis (60%). The pituitary MRI was without abnormality, the caryotype was normal 46, XX put under substitution treatment. The upper fibroscopy was normal. ECG and cardiac ultrasound were normal. Osteodensitometry revealed osteoporosis of the lumbar spine and osteopenia of the hip. Colonoscopy was normal. The genetic study did not show a C282Y mutation of the HFE gene. The patient is treated weekly by phlebotomy: 7cc / kg for a period of 09 months, the current ferritin is 49mg / l and the disease is reviewed in consultation every 03 months.

Case 3

B.A, 56 years old. Brother of the 02 patients. Diabetic Type II under insulin complicated by macropathy, chronic alcoholism. The clinical examination is without particularity. ferritinemia at 2604 mg / l, serum iron: 2. 53 mg / l, CST= 100%, HVC-HVB negative. Abdominal ultrasound was normal. Hepatic MRI found a severe hemochromatosis with CHF estimated using the T1-weighted sequence: 340 (+/- 50) umol / g, as well as a chronic pancreatitis. The colonoscopy objectified 02 millimeteric polyps with uncomplicated colonic diverticulosis. The histology shows a tubular adenoma in low grade dysplasia. Tumor markers: Ca19-9 = 75IU / ml, ACE = 5.12ng / mL. ECG and echocardiography: normal. Liver biopsy shows a parenchymal hemosideric overload (Searle-modified Roze score 3+) compatible with genetic hemochromatosis with severe portal fibrosis with some septa. The patient is treated with weekly by phlebotomy and the current ferritin is 99 mg / l .

DISCUSSION

Hereditary hemochromatosis (HHC) is an autosomal recessive disease that often occurs late. It is a chronic overload of iron of genetic origin that can affect a wide variety of organs and lead to potentially life-threatening. In Western Europe, the incidence varies from 2 to 5 ‰ people in France, up to 1% in Ireland [1]. Most of these patients have C282Y and H63D mutation in the HFE gene of chromosome 6p21.3. [2]. Hemochromatosis evolves in 4 phases ranging from clinical latency to the installation of visceral lesions. Once suspicion of hemochromatosis, ferritinemia and transferrin saturation (CTF) are routinely requested. HFE genetic tests should be performed only if the (CTF) is increased > 50%. At the same time, an inflammatory or neoplastic state, hemolytic, transfusional, infectious state or a metabolic syndrome must be eliminated before hyperferritinemia . The dosage of serum iron is not little interesting because it's variable in the day (higher than 30% in the morning). Hepatic MRI accurately estimates liver iron overload in the range of 50 to 350 mmol / g with a sensitivity of 84 to 91% and a specificity of 100%, but it is not possible to determine if hepatic fibrosis exists [3]. Liver biopsy still plays a role in the evaluation of hepatic fibrosis. The negative predictive value of serum ferritin <1000 mg / L and normal ASAT in the absence of hepatomegaly for the presence of severe fibrosis or cirrhosis was 95% on average [4]. Therefore it is indicated if the ferritinemia is greater than or equal to 1000 g / L, the transaminases are above the norm and the platelet count is less than or equal to 200 000 / mm3, since the risk hepatic cirrhosis is> 80% [5]. The diagnostic is confirmed by the discovery of mutations of the HFE gene (C282Y, H63D) homozygous or heterozygous type . But HHC phenotypes are observed in other genotypes. In 2018 the genetic test (HFE) can be prescribed as soon as the CS-Tf> 45%, confirmed on a 2nd test [6]. In a Caucasian population study, the homozygous C282Y mutation was found in 3% of people with hyperferritinemia [7]. Penetrance is highly variable estimated between 20% and 50% depending on the different characteristics of the study population. The mutation C282Y is insufficient for the disease to be expressed, environmental factors (alcohol, virus C, metabolic syndrome) or genetic often intervene [1]. The H63D mutation is more common than the C282Y mutation. The incidence of this homozygous mutation is about 2%, 23% for the heterozygous mutation. This mutation is not accompanied by significant iron overload [8]. Composite heterozygosity C282Y / H63D is rarely accompanied by clinical signs suggestive of overload (0.5-2%) [9]. Moderate ferritinemia (<500 µg / L), as well as transferrin saturation (less than 65%), or additional factors should be investigated [9]. in heterozygotes C282Y for the HFE gene, rare HFE mutations exist as S65C have been identified. In addition, other gene mutations of non-HFE hemochromatosis (TFR2, SLC40A1, HJV) could be sought after exclusion of homozygosity C282Y [3]. In the general population, routine genetic screening of HFE-HC is not recommended. Genetic counseling mainly concerns the siblings of the patient according to the HAS. It includes the determination of CS-Tf and ferritinemia or genetic (HFE test). In a subject who is heterozygous for the C282Y mutation, no follow-up is necessary unless there is overload [10]. In colorectal carcinogenesis many studies have emphasized the role of iron. In addition to excessive iron consumption, mutations of the HFE gene in patients with HH are associated with an increased risk of colorectal cancer (CRC). Similarly, examination of resected polyps and (CRC) showed that progression to CRC was associated with increased expression of iron import proteins and decreased expression of iron export proteins [11] . Hence an excess of intracellular iron can stimulate the growth of tumor cells. For heterozygosity for an HFE gene the mechanism is not known. The risk was higher in patient with excess iron intake, as well as in patients over 70 years of age. In contrast, a study of 229 patients with sporadic colorectal carcinoma revealed that heterozygosity for the C282Y mutation does not appear to be a risk factor for colorectal carcinoma [14]. The HFE gene responsible for excess iron promotes the development of colorectal adenomas more than those with normal or weak reserves [12]. Other study does not support this relationship [13]. Primary hepatocellular carcinoma is 200 times more common in hemo-chromatic patients, most commonly occurring in cirrhosis of the liver. Other extrahepatic cancers have been reported, including oesophageal cancer, melanoma, and lung cancer, gastric and hematologic cancers [14]. The treatment of HHC is based on repeated bleeding with the objective of achieving a ferritin level of less than 50 µg/L [15]. Asymptomatic homozygous C282Y patients have a life expectancy identical to the general population. Those with diabetes or cirrhosis have a reduced life expectancy, improved by regular phlebotomy [16]. The main causes of death

are diabetes, cardiomyopathy, hepatic insufficiency secondary to cirrhosis and hepatocarcinoma [9, 16]. Thus, thanks to the early biological diagnosis, Bloodletting is started early and serious complications should now become rarer.

CONCLUSION

The genetic hemochromatosis responsible for a ferric overload is most often related to a homozygous C282Y mutation. Family screening concerns siblings by the saturation factor of transferrin. It remains to be seen whether a strong correlation between the C282Y heterozygous state and distinct pathological conditions will exist and large-scale genotyping studies will help identify this potential risk in the future.

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