JUVENILE PRIMITIVE HEMOCHROMATOSIS WITH CARDIOMYOPATHY DEBUT. CASE REPORT

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Abstract: Juvenile hemochromatosis represents a rare entity, caused by mutation of HFE2 gene-situated on chromosome 1 or HAMP gene-situated on chromosome 19, that, characteristically occurs in the first up to the third decade of life. Cardiomyopathy is frequent in these patients and sometimes is the path to diagnose the disease. Also, it represents the main cause of death. The authors expose the case of a patient diagnosed with juvenile hemochromatosis, with multiple organic involvement. The disease debuted with dilatative cardiomyopathy, involving the excitoconductor system (complete atrioventricular block with syncope). Despite all adequate therapeutic measures clinical outcome was severe, with patients death.

INTRODUCTION

Juvenile hemochromatosis represents a rare entity, that usually occurs in the first up to third decade of life. First description of the disease was accomplished and published in 1932 by Bezançon et al[1]. The disease is caused by a mutation of HFE2 gene, also known as HIV (no connection with HFE genes)-located on chromosome 1 or mutation of HAMP gene-located on chromosome 19[2,3,4].

Juvenile hemochromatosis is characterised by iron overload in several organs and tissues. Clinical features vary from latent, asymptomatic forms (one third of patients are asymptomatic when they are diagnosed), to clinical symptomatic forms. Clinical presentation include severe asthenia-asthenemia syndrome, bone and joint changes (due to diffuse osteoporosis, subchondral arthropathy and joint chondrocalcinosis-radiographs findings), liver changes, diabetes mellitus, hyperpigmentation, dilatative cardiomyopathy, pituitary insufficiency, infectious manifestations. To these patients major iron deposition occurs in liver, with clinical features that vary from simple cytolysis to cirrhosis and hepatocellular carcinoma. Latent/asymptomatic forms are difficult to be diagnosed, an important role being attributed to laboratory and imagistic findings. An exact diagnose in this stage of the disease would be ideal in order to remove iron overload and to prevent irreversible organic failure[5,6,7].

CASE REPORT

We present the case of a male adolescent, aged 17 years old, that came to our clinic for: asthenia-asthenemia syndrome, lack of appetite, weight loss, posprandial abdominal pain and distension, joint pain, prolonged heartache, palpitations, symptoms that debuted/started 4 years before patient was admitted to our hospital. Previously the patient was hospitalized in a Pediatric Care Center for repeated Adams-Stokes syncope-electrocardiograms showed complete atrioventricular block, with escape ventricular rhythm, with escape ventricular rhythm, with escape ventricular rhythm.

At admission in our service the patient had an altered general status, hyperpigmentation, severe global heart failure, ascites.

Laboratory findings showed: erytrocyte sedimentation rate, reactive protein C-normal values; rheumatoid factor and antinuclear antibodies-absent; we found out slightly polyglobulia; liver tests indicated medium cytolysis, hyperbilirubinemia, hypoalbuminemia, hypergammaglobulinemia, decreased hepatic cholinesterase; repeated assesment of glycemia indicated normal values. Serum iron concentration value of 95 µmol/l; transferrin saturation of 70% and serum ferritin of 860 ng/ml confirmed the suspected diagnosis: hemochromatosis. Abdominal ultrasound showed liver cirrhosis, medium cuantity ascites. Paracentesis fluid was clear, with lymphocytes predominance; bacteriological tests were negative and cytology did not find tumor cells. Electrocardiogram indicated efficient cardiostimulation type VVI (Medtronic) was set up. Debut of the disease is characterized by iron overload and several organs and tissues. Clinical features vary from latent, asymptomatic forms (one third of patients are asymptomatic when they are diagnosed), to clinical symptomatic forms. Clinical presentation include severe asthenia-asthenemia syndrome, bone and joint changes (due to diffuse osteoporosis, subchondral arthropathy and joint chondrocalcinosis-radiographs findings), liver changes, diabetes mellitus, hyperpigmentation, dilatative cardiomyopathy, pituitary insufficiency, infectious manifestations. To these patients major iron deposition occurs in liver, with clinical features that vary from simple cytolysis to cirrhosis and hepatocellular carcinoma. Latent/asymptomatic forms are difficult to be diagnosed, an important role being attributed to laboratory and imagistic findings. An exact diagnose in this stage of the disease would be ideal in order to remove iron overload and to prevent irreversible organic failure[5,6,7].

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tricuspid valves medium insufficiency, moderate pericardial effusion were also noticed; Doppler examination of transmittal flow indicated an altered diastolic performance.

Bone and joint radiology showed diffuse osteoporosis, with minimal signs of subchondral arthropathy of the limbs.

Treatment was complex, including heart failure therapy (cardiotonics, diuretics, angiotensin converting enzyme inhibitors, beta-blockers), hepatoprotectors. Hemochromatosis therapy included: dietary regimen, blood removal (500 ml per week)-up to obtaining a normal value of serum iron and transferrin saturation. Patient outcome was unfavourable, with patient’s death (it occurred due to worsen cardiac failure, resistant to treatment). Family inquiry was negative.

**DISCUSSION**

There are several types of hemochromatosis, that are differentiated by genetic, biochemical and clinical features [8,9,10]. Type 1 hemochromatosis, most common form and type 4 are mostly seen in adults, type 2-juvenile hemochromatosis, type 3 hemochromatosis and neonatal hemochromatosis. Each type of hemochromatosis is caused by a specific genetic mutation. Type 1, 2 and 3 are inherited in an autosomal recessive manner and type 4 in an autosomal dominant manner; it is yet unknown how neonatal hemochromatosis is carried on.

For type 1 were ascertained genetic mutation of HFE gene (H=hemochromatosis, FE-ferrum), located on chromosome 6 (6p21.3). Federer et al described mutation C82Y at this level, that is found in 85% of homozygotes patients with hemochromatosis[11]. After, other mutation at HFE gene were observed[12,13]. An absence of this mutation usually denies the diagnosis of inherited hemochromatosis, except a number of cases identified in Italy[14,15]. Type 2 hemochromatosis is caused by mutation at HFE2 gene, also named HJV[15,16]. located on chromosome 1, or at HAMP gene, located on chromosome 19[17]. An essential role in establishing a positive diagnosis is played by an increased value of transferrin concentration (over 45%; the sensitivity of the method is over 95%); this parameter does not offer any information on iron deposits (serum ferritin is useful, but has no specificity for diagnose disease)[18]. Final diagnosis is sustained by specifying the existence of genetic mutation. Unfortunately we did not have the opportunity of establishing a genetic diagnosis, but clinical features and laboratory test clearly indicated the diagnosis of juvenile hemochromatosis (type 2 if we consider the age of debut). Cardiomyopathy is frequently seen in these patients and, in some cases, it represents the path to diagnose the disease[19,20].

Differential diagnosis of hemochromatosis implies hereditary and nonhereditary diseases that evolve with iron deposition. Hereditary entities include: hereditary aceruloplasminemia (autosomal recessive disease that evolves with diabetes mellitus, chronic hepatopathy, damage of central nervous system and retina)[21], hereditary ataxiasferrinemia. Uninherited diseases: excessive iron intake, chronic hepatopathies (chronic viral hepatitis C, cirrhosis, alcoholism), blood diseases (dyserthropoiesis, late cutaneous porphyria, hemolytic anemias-thalassemia, sideroblastic anemias), dysmetabolic liver siderosis (usually occurs in men with dysmetabolic syndromes-obesity, dyslipidemia, diabetes mellitus and it is characterised by liver massive iron overload, with consequent steatofibrosis).

Primitive hemochromatosis treatment consist in blood removal, initially more frequent for iron deposits removal and then periodically through lifetime. Therapy should be started as soon as possible to prevent liver cirrhosis.[22,23,24] Asthenia, adynamia, abdominal pain, cardiac and joint manifestations, diabetes mellitus may be influenced by treatment. Endocrine insufficiency is irreversible[25,26,27,28]. A family inquiry is extremely important in order to discover earlier family members affected by the disease.

Therapy that implies iron chelators (Deferoxamina) is not recommended for juvenile hemochromatosis, but for secondary iron overload. In patients who associate anemia or severe heart failure treatment with Deferoxamina may be indicated, alone or together with Deferiprone-this therapeutic attitude may reduce mortality by influencing left ventricle ejection fraction[29].

**CONCLUSIONS**

Juvenile hemochromatosis is a severe disease that may cause death. When diagnosing cardiomopathy, whether or not associated with severe arrhythmias, one should always think of juvenile hemochromatosis-further, an early adequate therapy may prevent complications and death.

**REFERENCES**