JUVENILE PRIMITIVE HEMOCHROMATOSIS WITH CARDIOMYOPATHY DEBUT. CASE REPORT

G. SUR [1], LUCIA BURAC[2], LUCIA SUR[3], LIANA KUDOR-SZABADI[4], D. SUR[5]

[1,5] University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, [2,3,4] Emergency Clinical Hospital for Children Cluj-Napoca

Keywords: *juvenile primitive hemochromatosis, cardiomiopathy*

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.*

Cuvinte cheie: *hemocromatoza primitivă juvenilă, cardiomiopatie*

Rezumat: *Hemocromatoza juvenilă reprezintă o entitate rară, cauzată de mutaţia genei HFE2-situată pe cromozomul 1 sau a genei HAMP-situată pe cromozomul 19, care, în mod caracteristic, se manifestă în prima pânã în treia decadă de viaţă. Cardiomiopatia este frecventă la aceşti pacienţi, reprezentând, în unele cazuri, calea spre diagnosticul bolii. De asemenea, afectarea cardiacă constituie şi principala cauză de deces. Autorii prezintă cazul unui pacient diagnosticat cu hemocromatoză juvenilă, cu implicare organică multiplă. Debutul bolii s-a realizat prin cardiomiopatie dilatativă, interesând sistemul excitoconductor (bloc atrioventricular complet cu sincopă). În ciuda aplicării metodelor terapeutice corespunzătoare, evoluţia clinică a fost severă, cu decesul pacientului.*

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 HJV (no connection with HFE genes)-located on chromosome 1 or mutation of HAMP gene-located on chromosome 19[2,3,4].

Juvenile hemocromatosis 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 symtomatic forms. Clinical presentation include severe asthenia-adynamia 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 cytolisis to cirrhosis and hepatocellular carcinoma. Latent/asymptomatic forms are difficult to be diagnosed, an important role being atributted 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-adynamia 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 pacient was hospitalized in a Pediatric Care Center for repeated Adam-Stockes syncope-electrocardiograms showed complete atrioventricular block, with escape ventricular rhythm-permanent cardiostimulation type VVI (Medtronic) was set up. During the last two years was ascertained a progressive abdominal distension and paroxysmal nocturnal dyspnoea. During last months the pacient complaint of increased joint, upper and lower limbs pain.

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 foud out slightly polyglobulia; liver tests indicated medium cytolisis, hyperbilirubinemia, hypoalbuminemia, hypergammaglobulinemia, decreased hepatic cholinesterase; repeated assesment of glycemia indicated normal values. Serum iron concentration value of 95 µmoli/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 pacemaker rhythm. Thoracic radiograph indicated global cardiomagaly, an hypokinetic heart and pulmonary stasis. Cardiac ultrasound confirmed dilatative cardiomyopathy: all heart cavities were expanded, with global hypokinesia of heart walls and a ventricular ejection fraction of 29%; mitral and

[1] Corresponding Author: Genel Sur- 25, Onisifor Ghibu street, Cluj-Napoca, e-mail: surgenel@yahoo.com; tel +40-0724504964
Article received on 28.04.2011 and accepted for publication on 08.08.2011
ACTA MEDICA TRANSILVANICA September 2011; 2(3)343-345

tricuspid valves medium insufficiency, moderate pericardial effusion were also noticed; Doppler examination of transmitral 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 occured due to worsen cardiac failure, resistant to treatment). Family inquiry was negative.

DISSCUSION

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 out 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]. 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 deposites (serum ferritin is useful, but has no specificity for diasease diagnose)[18]. Final diagnosis is sustained by specifying the existance 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], as it happened in our case. Data existing in literature name cardiac involvement as main cause of death for these patients, as seen in our case[20].

Differential diagnosis of hemochromatosis implies hereditary and nonhereditary diseases that evolve with iron deposition. Hereditary entities include: hereditary aceruloplasminemia (autosomal recessive disease thet evolves with diabetes mellitus, chronic hepatopathy, damage of central nervous system and retina)[21], hereditary atransferrinemia. Uninherited diseases: excessive iron intake, chronic hepatopathies (chronic viral hepatitis C, cirrhosis, alcoholism), blood diseases (dyserythropoiesis, late cutaneous porphyria, hemolytic anemias-thalassemia, sideroblastic anemias), dysmetabolic liver siderosis (usually occurs in men with dysmetabolic syndrome-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 deposites removal and then periodicaly 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 extremly 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].

CONLUSIONS

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

REFERECES

1. Bezançon F., De Gennes L., Delarue J., Oumensky V. Cirrhose pigmentaire avec infantilisme, insuffisance cardiaque et aplasies endocriniennes multiples. Bull Mem Soc Med Hop Paris, 1932; 48: 967-74.
2. Wain H.M., Bruford E.A., Lovering R.C., Lush M.J., Wright M.W., Povey S. Guidelines for human gene nomenclature. Genomics, 2002; 79: 464-70.
3. Rivard S.R., Lanzara C., Grimard D. Juvenile hemochromatosis locus maps to chromosome 1q in a French Canadian population. Eur J Hum Genet 2003; 11: 585-89.
4. Papanikolaou G., Samuels M.E., Ludwig E.H. Mutations in HFE2 cause iron overload in chromosome 1q-linked juvenile hemochromatosis. Nat Genet 2004; 36: 77-82.
5. Camaschella C. Understanding iron homeostasis through genetic analysis of hemochromatosis and related disorders**.** Blood, 2005 December; 106 (12): 3710-717.
6. Ma A.D., Udden M.M. Iron metabolism, iron overload, and the porphyrias. ASH Self-Assessment Program 2007 January; 2007 (1):6 -77.
7. Robson KJH, Merryweather-Clarke A.T, Cadet E., Viprakasit V., Zaahl M.G., Pointon J.J. et all. Recent advances in understanding haemochromatosis: a transition state. J Med Genet 2004, October; 41 (10): 721-30.
8. Militaru M.S., Popp R.A., Trifa A.P**.** Homozygous G320V Mutation in the HJV Gene Causing Juvenile Hereditary Haemochromatosis Type A. A Case Report. J GLD 2010 June; 19 (2): 191-93.
9. Gehrke S.G., Pietrangelo A., Kaščàk M. HJV gene mutations in European patients with juvenile hemochromatosis. Clin Genet 2005; 67: 425-8.
10. Le Gac G., Scotet V., Ka C. The recently identified type 2A juvenile haemochromatosis gene (HJV), a second candidate modifier of the C282Y homozygous phenotype. Hum Mol Genet 2004; 13: 1913-18.
11. Feder JN et al. A novel MHC class I like gene is mutated in patients with hereditarz hemochromatosis. Nat Genet 1996; 13: 399-408.
12. Deugnier Z., Moirand R., Guzader D., Jouanolle A.M., Brissot P. Surcharges en fer et gene HFE.Gastroenterol Clin Biol 1999; 23: 122-31.
13. Bacon B.R., Powell L.W., Adams P.C., Kresina T.F., Hoofnagle J.H. Molecular medicine and hemochromatosis: at the crossroads. Gastroenterology 1999; 116: 193-207.

14. Pietrangelo A et all. Hereditary hemochromatosis in adults.N Engl J Med 1999; 341: 725-32.
15. Roetto A., Totaro A., Cazzola M. Juvenile hemochromatosis locus map to chromosome 1q. Am J Human Genet 1999; 64: 1388-93.
16. Camaschella C., Roetto A., Cicilano M., Pasquero P., Basio G., Gubetta L et all. Juvenile and adult hemochromatosis are distinct genetic disorders. Eur J Hum Genete 1997; 1997: 371-5.
17. Morita H., Ikeda S.I., Yamamoto K. Hereditary ceruloplasmin deficiency with hwmochromatosis. Ann Neurol 1995; 37: 646-56.
18. Durupt S., Durieu I., Nove-Josserand R. L'hemochromatose genetique.Rev Med Internne 2000; 21: 961-71.
19. Filali M., Le Jeunne C., Durand E., Grinda J.M., Roetto A., Daraio F et all. Juvenile hemochromatosis HJV-related revealed by cardiogenic shock. Blood Cells Mol Dis 2004; 33: 120-4.
20. De Gobbi M., Roetto A., Piperno A., Mariani R., Alberti F., Papanikolaou G et all. Natural history of juvenile haemochromatosis. Br J Haematol 2002; 117: 973-9.
21. Mc Donnell S.M., Preston B.L., Jewell J.A., Barton J.C., Edwards C.Q., Adams P.C. et all. A survey of 2851 patients with hemochromatosis: symptom s and response to treatment. Am J Med 1999; 106: 619-24.
22. Adams P.C., Kertesz A.E., Valberg L.S. Clinical presentation of hemochromatosis: a changing scene. Am J Med 1991; 90: 445-9.
23. Andrews N.C. Disorders of iron metabolism. N Engl J Med 1999; 341: 1986-95.
24. Gerbaux A. La cardiomyopathie dilatee primitive. Medicorama 1992; 294: 17-21.
25. Barton J.C., Mc Donnell S.M., Adams P.C. Management of hemochromatosisi. Ann Internal Med 1998; 129: 932-9.
26. Crawford D.H., Halliday J.W. Current concepts in rational therapy for hemochromatosis. Drugs 1991; 41: 875-82.
27. Fargion S., Mandelli C., Piperno A. Survival and prognostic factors in 212 italian patients with genetic hemochromatosis. Hepatology 1992; 15: 655-9.
28. Lee P.L., Beutler E., Rao S.V., Barton J.C. Genetic abnormalities and juvenile hemochromatosis: mutations of the HJV gene encoding hemojuvelin. Blood 2004; 103 (12): 4669-71.
29. Fabio G., Minonzio F., Delbini P., Bianchi A., Capellini MD. Reversal of cardiac complications in a patient affected by a severe type of juvenile hemochromatosis. Blood 2007; 109: 362-4.