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Non-compaction and Polyneuropathy in a Patient Homozygous for the H63D HFE Gene Mutation

Case Report

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Abstract: Left ventricular hypertrabeculation/non-compaction (LVHT) is a cardiac abnormality that is increasingly reported with an association to several genetic disorders. We report an association of LVHT with genetically confirmed hemochromatosis and polyneuropathy in a 54-year old Caucasian female.

Keywords: *Non-compaction • Polyneuropathy • Hemochromatosis • Cardiomyopathy*

1. Introduction

Left ventricular hypertrabeculation/non-compaction (LVHT) is a cardiac abnormality which is increasingly reported with an association to several genetic disorders [1, 2]. The association of LVHT with genetically confirmed hemochromatosis and polyneuropathy has not been described before.

2. Case Report

A 54-year-old Caucasian female's echocardiography, performed because of arterial hypertension, disclosed normal-sized cardiac cavities and a slightly thickened left ventricular wall. In the apex, the myocardium had a 2-layered structure consisting of a compacted outer and a non-compacted inner layer. Four trabeculations were found apically from the insertion of the papillary muscle, which were consistent with the diagnosis of LVHT (Figure 1). The systolic functions was normal with an ejection fraction of 60%, but Doppler-sonography showed signs of disturbed relaxation. She had a history of arterial hypertension and ataxic gait disturbance since two years prior. Because of a peripheral arterial occlusive disease, a stent-implantation had been performed in the popliteal artery one year before. She had been drinking alcohol for 30 years. A hepatopathy was known since two years prior and was primarily assumed to be alcohol-induced. Two years ago, she suffered from diarrhoea for 5 weeks, received several antibiotics, and lost 20 kilograms of weight. Coloscopy revealed a probably antibiotic-induced colitis with toxin-positive *clostridium difficile*. At that time, her serum ferritin level was 712 ng/ml (normal being 15-150 ng/ml), serum iron level was 111 µg/dl (normal being 40-150 µg/dl), transferrin level was 100 mg/dl (normal 200-360 mg/dl), and transferrin saturation level was 79% (normal being 16-45%). Hemochromatosis was suspected and genetic studies found her to be homozygous for the H63D mutation of the HFE gene. Since then, she underwent phlebotomies at an interval of 8-12 weeks. One year ago, she was hospitalised because of anginal chest pain. Coronary angiography showed no stenoses and the chest pain was assumed to be caused by hypertensive episodes. Clinical neurologic investigation revealed sore neck muscles, slight distal weakness (M5-) of the upper limbs, and slight diffuse weakness (M5-) of the lower limbs. There was an obvious wasting of the thighs but fasciculations were absent. The tendon reflexes were

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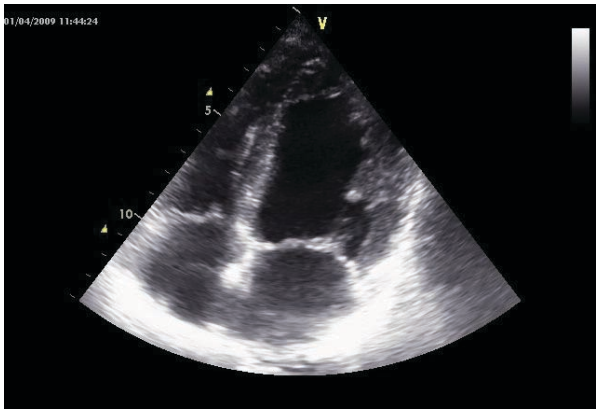
Figure 1. The echocardiographic apical four-chamber-view shows the left ventricular hypertrabeculation/non-compaction affecting the lateral and apical walls of the left ventricle. A 2-layered structure of the myocardium with a compacted outer and a non-compacted inner layer is visible in the apex and 4 trabeculations are visible apically from the insertion of the papillary muscle.



brisk and pyramidal signs were positive. There was no sensory deficit, but gait and stance were markedly ataxic. Except for an increase in aldolase, the muscle enzymes were within their respective normal ranges. Nerve conduction studies showed a slight reduction in the motor and sensory nerve conduction velocities and reduced amplitude of the compound muscle and sensory action potentials. Needle electromyography was only non-specifically abnormal. Cerebral magnetic resonance imaging scan showed periventricular and subcortical gliotic spots bilaterally. A muscle biopsy, carried out to look for iron deposition in the skeletal muscle, showed slight myopathic changes and subsarcolemmal accumulation of PAS-positive material, but also showed normal activity of glycolytic enzymes. She was advised to stop the alcohol and nicotin abuse in order to take sertralin, ramipril, and lansoprazole.

3. Discussion

Hemochromatosis may be due primarily to an increase in iron absorption by the gastrointestinal tract and due secondarily to an overload in iron in various hematologic disorders. HFE-associated hereditary hemochromatosis is the most common type of inherited iron overload disorder. An inappropriate low secretion of hepcidin, which would negatively regulate iron absorption, is postulated to be the mechanism for iron overload in this condition. The characteristic biochemical abnormalities are elevated serum transferrin-iron saturation and serum ferritin. Typical clinical manifestations include cirrhosis, liver fibrosis, hepatocellular carcinoma, an elevated serum aminotransferase level, diabetes mellitus, restrictive or dilative cardiomyopathy, and arthropathy. The two principal means of treatment by iron depletion are phlebotomy in primary hemochromatosis and excretion of iron by chemical chelation in secondary hemochromatosis.

Cardiac involvement in hemochromatosis affects mainly the myocardium: iron overload of the myocytes reduces left ventricular distensibility. Heart failure is the most frequent manifestation of cardiac involvement. Diagnosis of cardiac involvement depends essentially on the Doppler echocardiography showing abnormal left ventricular filling and, later, ventricular dilatation with left ventricular systolic dysfunction. The age at which symptoms and specific organ involvement appear in hemochromatosis depend on the type of mutation.

Recently, LVHT has been diagnosed in identical twins with thalassaemia and secondary hemochromatosis who were receiving iron chelation therapy in the form of desferrioxamine [3]. Like in our case, it remained uncertain in these cases whether LVHT was caused by iron overload or whether this association was coincidental. LVHT has also been reported in children with methylmalonic aciduria and homocystinuria, an inborne error of cobalamin metabolism [1], and in a young female with cystinosis [2].

Effects of the nervous system by the iron overload include encephalopathy due to deposition of iron within neurons and glial cells, and deposition of the excessive iron overload in the peripheral nerves and the skeletal muscle. The latter may give rise to the development of polyneuropathy and myopathy [4,5]. In the presented patient, there were indications of axonal polyneuropathy and metabolic myopathy, but whether these abnormalities were due to the iron overload, due to the chronic alcohol abuse or due to a neuromuscular disorder associated with LVHT remains speculative. Most likely, polyneuropathy is attributable to the chronic alcohol abuse since polyneuropathy due to hemochromatosis has been of the demyelinating type [5]. The lack of iron overload shown in the muscle biopsy may be explained by the phlebotomies that the patient underwent since two years prior.

This case shows that LVHT may be associated with hemochromatosis and that this association is rather coincidental, not causative.

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