ESC HEART FAILURE
ESC Heart Failure 2019; **6**: 228–231
Published online 8 January 2019 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12395

CASE REPORT

Cardiac arrest in Wilson's disease after curative liver transplantation: a life-threatening complication of myocardial copper excess?

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Abstract

We report the case of a 38-year-old man who presented with cardiac arrest 1 year after curative liver transplantation for Wilson's disease. Clinical work-up proofed myocardial copper and iron accumulation using mass spectrometry, which led most likely to myocardial fibrosis as visualized by cardiovascular magnetic resonance (unprecedented delayed enhancement pattern) and endomyocardial biopsy. Consequently, cardiac arrest due to ventricular fibrillation and subsequent episodes of sustained ventricular tachycardia were considered as primary cardiac manifestation of Wilson's disease. This can, as illustrated by our case, occur even late after curative liver transplantation, which is an important fact that treating physicians should be aware of during clinical follow-up of these patients.

Keywords Wilson disease; Copper; Cardiac arrest; Ventricular arrhythmia

Received: 20 June 2018; Accepted: 15 November 2018
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Introduction

Wilson's disease (WD) is an autosomal recessive disorder with an estimated prevalence of 1/30,000. The disease is caused by mutations of the ATP7B gene on chromosome 13, which encodes for a P-type ATPase that is mainly expressed in the liver. The mutations lead to an impairment of the incorporation of copper into apoceruloplasmin and reduced excretion of copper into the bile.[1] The latter results in a continuous accumulation of copper in the liver, with subsequent cellular injury and tissue damage. A further consequence is the release of excess copper into the blood circulation, which results in the continuous deposition and subsequent toxic injury of other organs, as the increased urinary copper excretion is not fully able to compensate for the decreased biliary excretion.[1] Over time, the damage will potentially lead to the characteristic hepatic, neurological, ophthalmic, and/or psychiatric manifestations of WD. Rarely, accumulation of copper in the heart causes conduction abnormalities, arrhythmias, cardiomyopathy, and/or sudden cardiac death.[2,3]

Here, we describe an unprecedented case of cardiac arrest in a patient with WD 1 year after curative liver transplantation.

Case report

A 38-year-old man with cured WD due to liver transplantation collapsed during exercise. Emergency medical service was called instantly, and the patient was found to be in ventricular fibrillation upon their arrival. Advanced cardiopulmonary resuscitation was started immediately, and after approximately 8 min and a total of four defibrillations, sinus rhythm with subsequent spontaneous circulation was restored.

Upon arrival at the hospital, the patient was still unconscious and intubated but hemodynamically stable. The admission electrocardiogram revealed unspecific ST-T alterations that normalized within a few days (*Figure 1*). A bedside echocardiography study revealed a dilated left ventricle with global hypokinesia and reduced ejection fraction of 30%. An acute coronary angiography revealed normal epicardial vessels. Initial blood analysis showed the following relevant findings: sodium 139 mmol/L, potassium 2.9 mmol/L, lactate 1.9 mmol/L, high-sensitivity troponin T 17.5 ng/L, N-terminal pro-B-type natriuretic peptide 131 ng/L, and normal liver and renal function parameters. Subsequently, the patient received 24 h therapeutic hypothermia treatment, and normokalemia was restored. Two days later, he was weaned from mechanical ventilation and regained consciousness without any signs of neurological deficit.

A thorough medical history revealed no family history of cardiovascular disease or sudden cardiac death, nor any previous symptoms or signs suggesting progressive heart disease. At the age of 22, the patient had been diagnosed with WD and was subsequently treated with trientine and zinc sulfate for many years. Representative laboratory findings during the chelation therapy showed the following: 24 h urinary copper excretion 5 μmol/day (treatment target 3–8 μmol/day), S-ceruloplasmin 0.14 g/L (normal range 0.22–0.58 g/L), and S-copper 5.4 μmol/L (normal range 11–23 μmol/L). Despite chelation therapy, the liver function deteriorated gradually, which finally resulted in a liver transplantation 1 year before the cardiac arrest. Until then, the patient had no other known WD-related complications and is, otherwise, apart from a known psoriasis since the age of 15, completely healthy. The routine cardiac evaluations prior to liver transplantation were normal. A physical examination revealed no abnormalities.

After 3 days, a further echocardiographic exam revealed normalized cardiac dimensions and function. Additionally, the patient underwent a cardiovascular magnetic resonance exam (*Figure 2A–E*) and endomyocardial biopsy (*Figure 2F*), both showing areas of myocardial fibrosis but no signs of inflammation. Inductive coupled plasma mass spectrometry confirmed excessive deposition of copper and iron in the previously taken endomyocardial biopsy sample: copper 10.1 μg/g wet weight (normal range 2.46–4.13 μg/g) and iron 163.3 μg/g wet weight (normal range 35.2–71.3 μg/g).[4] Right heart catheterization revealed normal findings. Finally, an implantable cardioverter defibrillator was successfully implanted, and the patient was discharged from hospital.

During the last 20 months following discharge, the patient experienced a total of eight episodes of sustained ventricular tachycardia all successfully treated by antitachycardia pacing and/or shock therapy (*Figure 3*). Because all episodes were triggered by exercise, two stress electrocardiograms were performed revealing no abnormalities. After the first ambulatory arrhythmia episode, treatment with bisoprolol was initiated and titrated up to the maximal tolerated dose of 7.5 mg/day. Despite medical therapy, the patient still experiences episodes of exercise-induced sustained ventricular tachycardia, but has been able to regain a normal work and social life. During follow-up, repetitive testing revealed stable potassium levels within the normal range without additional need for substitution.

Discussion

The pathogenesis of cellular injury due to copper accumulation is poorly understood. In hepatocytes, it has been shown

Figure 1 Resting electrocardiogram several days after cardiac arrest. Apart from a left anterior fascicular block (left axis deviation: −51°, QRS 90 ms), the resting electrocardiogram was normal.

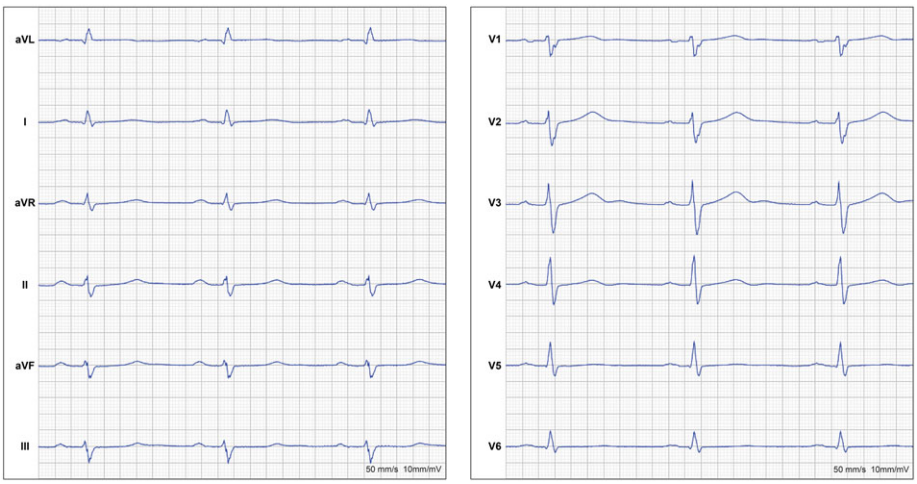

Figure 2 Cardiovascular magnetic resonance and endomyocardial biopsy. Cardiovascular magnetic resonance revealed multiple areas of intramural and subepicardial delayed enhancement (corresponding to fibrosis, as indicated by white arrows) in the short-axis (C), four-chamber (D), and two-chamber projections (E). Furthermore, there were no signs of oedema/inflammation (B; T2-weighted image), and the cardiac morphology and function was normal (A). These findings were confirmed by endomyocardial biopsy (F; Sirius staining showing areas of fibrosis in pink and the nuclei of myocytes in purple; no signs of inflammatory cell infiltration were present).

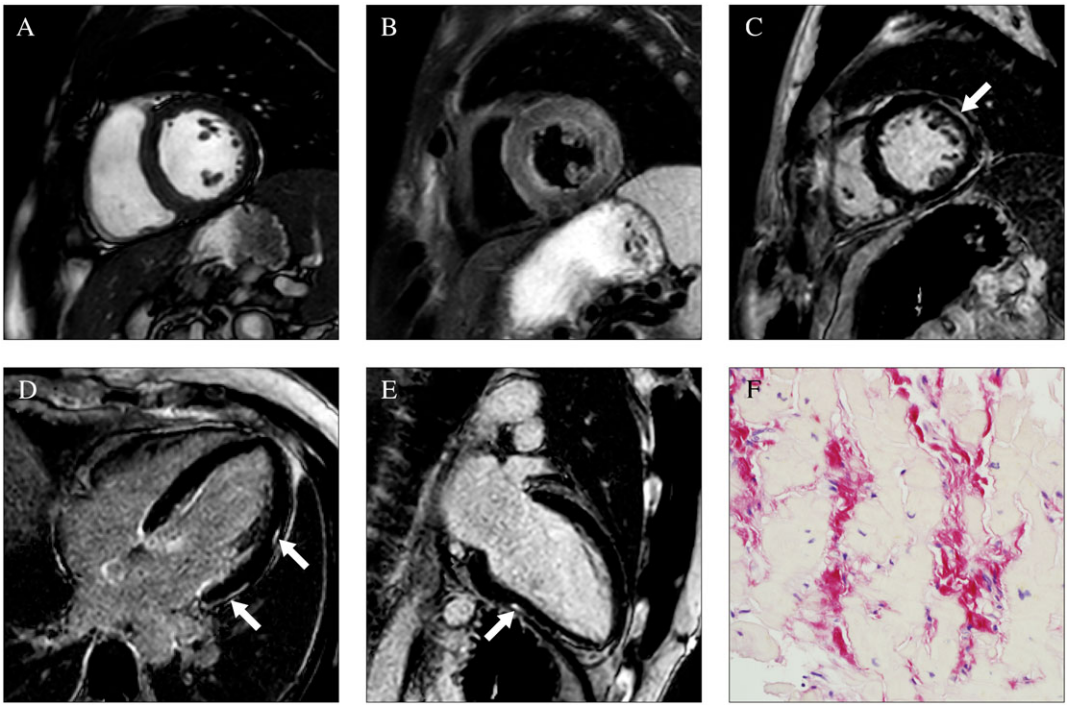

Figure 3 Ventricular tachycardia treated by implantable cardioverter defibrillator. The registration of the implantable cardioverter defibrillator shows the beginning of a ventricular tachycardia episode (left side), which was successfully treated by antitachycardia pacing (middle and right side).

that excessive copper-induced oxidative stress plays an essential role, resulting in mitochondrial dysfunction,[5] damage of DNA and lipid molecules, and inhibition of protein synthesis.[6] In the end, cellular death is likely to occur leading to a subsequent inflammatory response and the development of fibrosis.[7] Our knowledge concerning the pathogenesis of myocardial injury is even more scarce, but similar processes as observed in liver cells might be involved. This assumption is supported by an autopsy study by Factor *et al.*, who described the presence of focal inflammatory cell infiltration, fibrosis, and small vessel sclerosis in the myocardium of patients with WD.[8] A further potential factor that can contribute to cellular injury is the simultaneous myocardial accumulation of iron in patients with WD, as the copper-binding protein ceruloplasmin plays a pivotal role in iron metabolism.[9]

In our patient, we were able to proof the presence of myocardial copper and iron accumulation using inductive

coupled plasma mass spectrometry, which led most likely due to the previously described processes to the development of myocardial fibrosis and a subsequently increased cardiac vulnerability for ventricular arrhythmias. The presence of myocardial scar was confirmed by cardiovascular magnetic resonance, which revealed an unprecedented delayed enhancement pattern, as well as endomyocardial biopsy. Further contributing factors to the genesis of ventricular arrhythmias could have been the transient hypokalemia, immunosuppressive treatment with tacrolimus, and/or mitochondrial dysfunction caused by the increased myocardial copper concentration.[10] The hypokalemic episode itself could have been induced by the patient's immunosuppressive treatment with tacrolimus and mycophenolic acid, as no other underlying cause could be identified despite extensive evaluations. Finally, the process of myocardial injury might still continue even after curative liver transplantation, as the levels of copper and iron remain high for a longer time period due to the slow washout of metals from the myocardium.[11] This could also be a further reason for the recurrent ventricular arrhythmias in our patient, as mitochondrial dysfunction continues. Furthermore, we observed transient myocardial dilatation and dysfunction accompanying cardiac arrest, which was most likely caused by myocardial stunning secondary to hypoperfusion during ventricular fibrillation and/or the repetitive defibrillations.[12]

In conclusion, we considered the initial cardiac arrest due to ventricular fibrillation and the subsequent recurrent episodes of sustained ventricular tachycardia as primary cardiac manifestation of WD for which the patient received an implantable cardioverter defibrillator as well as treatment with beta-blockers. As our case illustrates, can cardiac manifestations of WD occur even late after curative liver transplantation. This is an important fact that treating physicians should be aware of during clinical follow-up of these patients.

Conflict of interest

None declared.

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