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CASE REPORT

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Sudden cardiac death in hereditary hemochromatosis: an underestimated cause of death?

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Abstract Hereditary hemochromatosis (HH) is a frequent autosomal recessive disease which causes iron-overload of various organs. Of all northern European affected individuals, 90–95% show 1 of 3 known point mutations in the HFE gene. Symptoms and organs involved can vary considerably: Only a small fraction of the 200,000–400,000 persons affected in Germany develop the classical picture of liver cirrhosis and/or pancreatic fibrosis. Nevertheless, the life expectancy of persons with moderate or even subclinical symptoms is reduced, in many cases due to myocardial damage leading to cardiomyopathy with greatly increased risk of sudden cardiac death. Although the high prevalence of HH suggests that sudden cardiac death due to cardiac HH is a relatively common cause of death, the forensic literature lacks such reports. We present the case of sudden cardiac death in a young man with histological findings of massive cardial hemochromatosis which is characterized by the fact that none of the three known mutations for HH were found. This case demonstrates that genetic screening alone might not be sufficient to identify all persons at risk to developing HH.

Keywords Hereditary hemochromatosis · HFE gene · Sudden cardiac death · Cardiomyopathy · Arrhythmia

Introduction

Hereditary hemochromatosis (HH) is an autosomal recessive disorder characterized by excessively high iron absorption from the gut resulting in iron overload [1]. HH is the most common inherited disease of Europeans with 1 in 200–400 affected (although many of them subclinically) and a carrier frequency approaching 10% [2, 3]. When diagnosed at an early stage, the condition responds well to a therapy consisting of repeated phlebotomy. However, without therapy the classical clinical course of HH is characterized by cirrhosis of the liver and fibrosis of the pancreas combined with brown skin coloration leading to a complex of symptoms termed "bronzed diabetes". Patients die 10 times more frequently from liver cirrhosis, 14 times more frequently from diabetes mellitus, and 119 times more frequently from liver cancer [4] than persons without this condition. On the other hand it is less well known that a high percentage of patients suffering from HH develop cardiomyopathy due to iron deposition in myocytes. A high percentage of patients develop congestive heart failure from both systolic and diastolic myocardial dysfunction [5] and the clinical course is dominated by malignant arrythmias, often leading to syncope and sudden cardiac death [6, 7, 8]. Of HH patients, 1 in 3 shows electrocardiographic changes, and death from cardiomyopathy is 14 times more frequent than expected [9]. The importance of iron metabolism for the heart is demonstrated by the fact that in a large cohort study an association with cardiovascular death was observed not only for homozygous persons, but also for heterozygous carriers of HH mutations [10]. Given the high prevalence of the disease, cardiac deaths in HH should thus be frequently diagnosed during medicolegal autopsies. Nevertheless, the forensic literature lacks reports of sudden death associated with HH. We would thus like to present the case of a 35-year-old man with the clinical diagnosis of "alcoholic" cirrhosis of the liver who was found to have died from sudden cardiac death due to HH with severe myocardial involvement. This case merits attention mostly for two aspects: firstly, it demonstrates that genetic screening alone might not be sufficient to identify all persons at risk to develop HH. Secondly, it highlights the discrepancy between the common clinical diagnosis of HH and the rare establishment of HH as cause of death upon medicolegal investigations.

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Case history

A 35-year-old man collapsed while riding a bicycle and was found dead at the scene of the accident. The police investigating the death were able to exclude an involvement of other persons in the death and the prosecutor released the body despite the fact that both manner and cause of death were undetermined by routine necropsy.

Upon second necropsy by a forensic pathologist, which is obligatory before cremation in Germany, minor hematomas and abrasions of the face were observed. The relatives stated that the decedent had had a "drinking problem" until 1 year before his death when an "alcoholic" cirrhosis of liver had been diagnosed during a routine check by an internist. The deceased had refrained from further drinking after that disclosure and had been in a state of relatively good health until a few weeks before his death when he started complaining to his mother about faintness, palpitations and lethargy. Ascites and peripheral oedema were treated successfully with diuretics. A routine medical check including routine laboratory parameters was non-specific, no signs of diabetes were found. No blood transfusion or external iron substitution was performed. The relatives agreed that an autopsy be performed to establish the cause and manner of death.

Findings at autopsy

The body was 183 cm in length, weighed 72 kg and was that of a white male of average build with marked hypostasis and already regressed rigor mortis. No injuries except for minor abrasions on the hands and the forehead were noted. The skin was unicteric, but of a peculiar grey-brown coloration.

The liver weighing 1,950 g showed pronounced micronodular cirrhosis. Signs of portal hypertension were a large spleen (430 g) and a single esophageal varicose vein, but no ascites was detected. The pancreas was inconspicuous. The heart weighing 350 g showed marked distension. No peripheral edema was noted and no ethanol was detected in blood and urine.

Histological examination

After standard hematoxylin-eosin staining, the liver sections showed micronodular cirrhosis with portal fibrosis containing slight inflammatory infiltration. Approximately 50% of the liver parenchyma was substituted by regenerate nodules. The liver cells contained abundant granular brown pigment which could be stained with prussian blue reagent in an iron staining method (Fig. 1). Moreover prussian blue positive granules were abundant in phagocytes and in bile duct epithelia. Iron was found in all other parenchymal organs of the deceased. Most impressive however was the deposition of iron containing granules in the myocardium (Fig. 2) combined with marked dilation and disconnection of the muscle fibres in all sections, as in dilatative cardiomyopathy. In one hematoxyline-eosin stained section a necrosis of a group of iron-containing muscle fibres surrounded by granulocytes indicating a fresh necrosis was found (Fig. 3).

DNA isolation and PCR

DNA was isolated from a dried blood stain using an alkaline lysis protocol [11]. To detect the known mutations PCR followed by restriction analysis was performed and the restriction enzymes cut the wild type, but not the known mutated variants. To identify the Cys282Tyr variant (nt 845, G to A) a 237 bp fragment of exon 4 of the HFE gene was amplified using the polymerase chain reaction and restricted using *SnaB*I as described [12].

To detect the rare His63Asp and Ser65Cys variants, a 294 bp fragment of exon 2 was amplified and restricted using *Mbo*I (His63Asp) and *Hinf*I (Ser65Cys) [13, 14]. The restricted ampli-

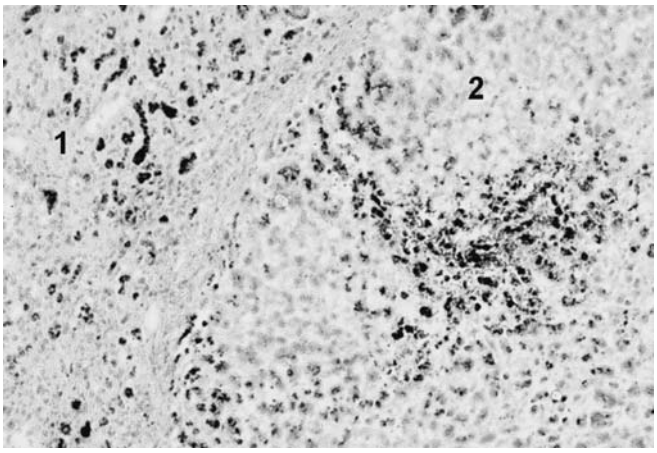

Fig. 1 Iron-stained section of the cirrhotic liver. The dark stained granules indicate iron deposition. "2" indicates a nodule with abundant iron stained hepatocytes and phagocytic cells, "1" indicates iron stained bile ducts in a fibrous septum

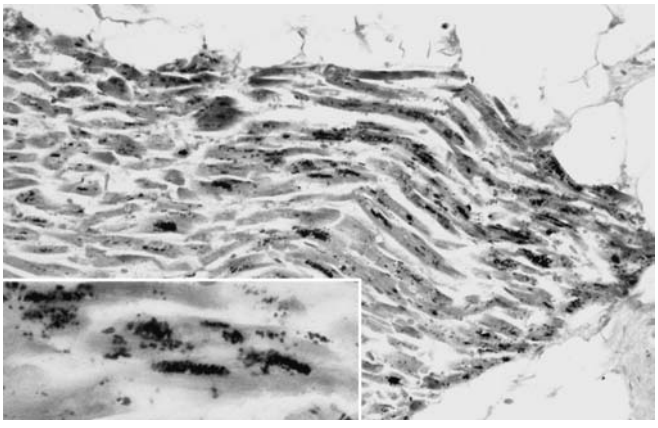

Fig. 2 Iron-stained section of the myocardium with extensive intracellular iron deposition. The insert shows an enlarged view of the central area (magnification 3×)

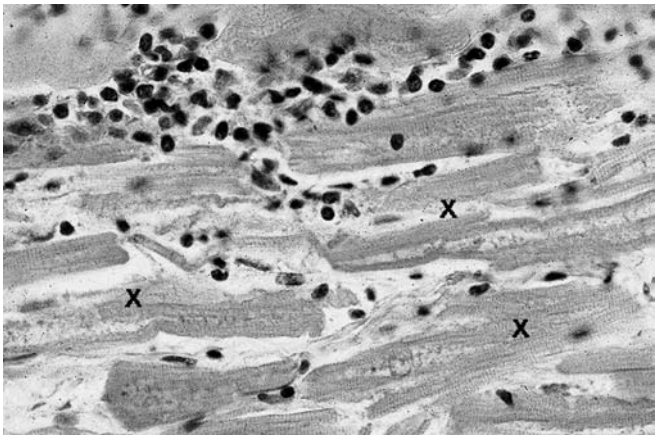

Fig. 3 Hematoxylin-eosin-stained section of the myocardium. Necrosis of single muscle cells with infiltration of phagocytotic cells. The "x" indicates cells with granular iron deposition (not stained)

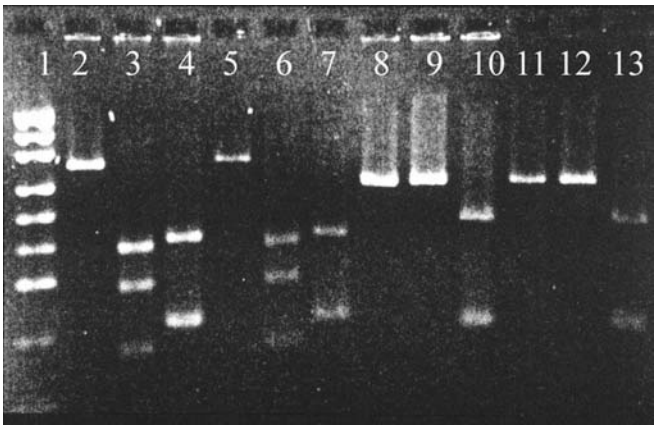

Fig. 4 Ethidium bromide-stained agarose gel of the digested PCR products for the HFE gene. *Lane* 1 size marker (fragment sizes: 500, 400, 300, 200, 175, 150, 125, 100, 75 bp), *lanes* 2–4 and 8–10 control DNA (healthy person), *lanes* 5–7 and 11–13 proband, *lanes* 2 and 5 amplicon for exon 2 (undigested), l*anes* 3 and 6 amplicon for exon 2 digested with *Mbo*I, *lanes* 4 and 7 amplicon for exon 2 digested with *Hinf*I, *lanes* 8 and 11 amplicon for exon 4 (undigested), *lanes* 9 and 12 amplicon for exon 4 digested with *SnaB*I, *lanes* 10 and 13 amplicon for exon 4 digested with *Rsa*I. As the control DNA (healthy person) showed the same restriction fragments as the tested person none of the three point mutations was detected

cons were separated by agarose gel electrophoresis and stained with ethidium bromide. As the amplificons of the tested person were restricted in all three assays, none of the three known gene variants were identified (Fig. 4).

Results and discussion

The presence of iron-containing particles in liver cells is a relatively non-specific finding in liver cirrhosis [15, 16]. In all cases except in hereditary hemochromatosis (HH), however, the iron deposition is confined to liver cells and phagocytic cells whereas bile duct epithelia are spared. Moreover, extensive iron deposition outside of the liver as seen in the present case is pathognomonic for HH provided that secondary iron overload due to multiple blood transfusions or excessive iron use is excluded [15]. As no iron substitutions or blood transfusions were performed in the present case, the diagnosis of HH was established based on the histological findings.

A genetic test for the three known point mutations in the HFE was performed to further investigate the case. The variants of this gene (formerly termed HLA-H) which is related to the MHC class I gene family, lead to an increased cellular iron absorption by interacting with the transferrin receptor and can be identified in the majority of HH patients in Caucasians. In our case, however, the genetic test was negative. Nevertheless, as approximately 5–10% of central and northern European patients with clinical signs of HH lack these variants [17], the diagnosis HH was maintained (in individuals of mediterranean origin the percentage of HH patients lacking these gene variants is even considerably higher).

Despite the relatively high percentage of false negatives (i.e. patients with HH but without one of the three known mutations) in genetic testing, HH is considered to be the ideal disorder to demonstrate the usefulness of genetic tests [18]: it is relatively frequent, can (mostly) be efficiently diagnosed using a simple genetic test, and iron depletion therapy is cheap and efficient. Repeated phlebotomy after a timely diagnosis ensures a life expectancy comparable to that of unaffected persons. However, in many cases no diagnosis can be established during lifetime as the symptoms develop late in affected persons and can vary considerably. Therefore it is, in our opinion, of importance that medicolegal autopsies lead not only to the establishment of manner and cause of death, but that also relatives who might be affected by the same disease are warned and suitable measures can be taken [19]. In the present case the sister of the deceased was advised to have the iron metabolism tested.

Hereditary hemochromatosis can affect several vital organs and is associated with a number of different causes of death. In the present case only moderate cirrhosis with sufficient hepatic parenchyma was found. Neither icterus nor ascites were observed. The case history contained neither bleeding from esophageal varicosis nor episodes of hepatic coma. Death could therefore not be attributed to liver damage or other direct consequences from cirrhosis. Also pancreatic damage leading to diabetes can be excluded, as an internistic check up 1 week prior to the death was negative in that respect.

On the other hand the myocardial findings were most impressive: The decedent showed massive iron deposition and marked dilation and disconnection of the myocardial fibres leading to reconstruction of the myocardial tissue. Moreover cellular necroses were observed.

Although damage to the liver and pancreas are the most prominent signs of HH, cardiomyopathy is a typical complication [4]. Of 69 deaths in German HH patients, 5 were attributed to cardiomyopathy, 14 times more than expected [9]. Recently 2 cases were reported in which cardiomyopathy was the only symptom leading to the diagnosis of HH [20]. Moreover, cardiac arrythmias appear to be prominent in cardiomyopathy related to HH [4, 5, 6, 7, 8, 9]. Considering these facts and the high prevalence of HH, it can be expected that sudden cardiac death due to HH should be a relatively frequent cause of death. However, the fact that the forensic literature lacks reports of such cases (whereas there are several reports of other, less common causes of cardiac death or sudden death from hereditary diseases [21, 22, 23, 24] suggests that this cause of death might not be established as often as it should be during medicolegal autopsies.

We therefore concluded that sudden cardiac death in the patient suffering from HH, related cardiomyopathy is the most probable cause of death. The fact that the patient lacked the three known gene variants corresponding to HH suggests that there are more, hitherto unidentified mutations and makes this case even more interesting, especially as a German health insurance company plans to offer a free genetic mass screening for its insurees [25]. This

case emphasizes that genetic screening alone cannot always identify patients at risk to develop HH.

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