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Case report

Liver cirrhosis associated with double heterozygosity for genetic hemochromatosis (H63D) and alpha-1 antitrypsin deficiency (M-Malton) – A case report

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Abstract

Genetic hemochromatosis (GH) and alpha-1 antitrypsin (AAT) deficiency (AATD) are two autosomal recessive disorders associated with an increased risk for liver injury. Among different AATD and GH genotypes, the M-Malton and the S variants are frequent in Sardinia, an Italian island of the Mediterranean Sea, suggesting that a possible relationship between these two metabolic disorders in chronic liver diseases should be considered. Here we report a case of liver cirrhosis associated with double heterozygosity for M-Malton AATD and H63D GH alleles. The histological observation revealed micronodular cirrhosis with focal micro- and macrovesicular steatosis with globules of AAT protein and iron overload. The clinical and laboratory picture led to listing the patient for orthotopic liver transplantation. Two sons, who were apparently healthy, on molecular testing showed a normal AAT genotype, whereas one of them was heterozygous for the H63D GH mutation. This clinical case underlines the importance of the diagnostic role played by the liver biopsy, in particular when rare genetic variants could be involved.

Keywords

Liver cirrhosis, alpha-1 antitrypsin deficiency, M-Malton, hemochromatosis, H63D, double heterozygosity.

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Introduction

Alpha-1 antitrypsin (AAT) deficiency (AATD) and genetic hemochromatosis (GH) are two autosomal recessive disorders associated with an increased risk for liver injury [1].

A recent study about polymorphisms of GH and AAT genes in the Egyptian population highlights the opportunity to perform specific genetic counseling in different populations in order to have better diagnosis, prognosis and treatment [2].

Since this protease inhibitor counteracts the detrimental effects of neutrophil elastase in lung alveoli, all the severe AATD variants are related to lung diseases, but only a few of these are also responsible for liver dysfunction. A change in the AAT protein conformation and a low efficiency of the protein-altered degradation pathway seems to be directly involved in the pathogenesis of liver disease in AATD subjects [1] and, recently, new AAT biological functions in iron metabolism were proposed [3].

Here we report a case of liver cirrhosis associated with double heterozygosity for M-Malton AATD and H63D GH alleles.

Among different AATD genotypes, the M-Malton variant is frequent in Sardinia, an Italian island of the Mediterranean Sea [4]. From a pathological point of view, the Pi M-Malton clinical expression mimics the Pi Z phenotype. The mutation of the Pi M-Malton variant is characterized by a TTC deletion of one of the two consecutive 51/52 codons encoding for a phenylalanine [4] located in a particular hot spot region (M-like region) and by a normal iso-electrophoretic pattern of the protein (M-like variant) [5]. For these reasons, some authors have suggested that this variant is probably not so rare, but rarely diagnosed [6].

GH is a metabolic disorder characterized by progressive systemic iron overload, leading to severe liver disease. Different molecular changes are associated with increased iron overload: 5 responsible genes have been identified, but the C282Y and H63D mutations of the *HFE* gene are reported in approximately 90% of GH cases in Northern Europe [7]. To date, homozygosity for the C282Y mutation is generally considered the main cause for the onset of GH [7]. On the contrary, the role of the H63D mutation in the expression of the disease is merely confined to the C282Y/H63D compound heterozygous state [8].

Only a few studies have explored the risk of liver disease in adult individuals with heterozygous AATD, suggesting that this genetic condition may represent an increased risk factor only when associated with other etiologic factors, including hepatitis C virus (HCV) infection, alcohol or drug abuse, GH [9].

Even if several pieces of evidence suggest that the presence of mild to moderate iron overload or AATD due to heterozygosity for the *HFE* or AAT mutations may act as co-factors for chronic liver diseases, the prevalence and the relevance of both these associations in the heterozygous state in liver disease progression are still overlooked [8]. A relation between AATD and *HFE* and an earlier development of cirrhosis was first proposed by Elzouki et al. [10].

Even if data on the coexistence of AATD and GH are controversial [11], it was suggested that AAT and iron metabolism might interact, causing increased liver storage of AAT and/or iron with a faster development of cirrhosis [12].

Here, for the first time, we describe a case of liver cirrhosis associated with double heterozygosity M-Malton/H63D with a concomitant liver storage of AAT protein and iron in liver cells.

Case presentation

A 50-year-old man, born in Sardinia, was admitted to our hospital with increasing weakness and fatigability, anorexia, weight loss and mild symptoms of liver disease. At admission, the patient did not report liver disease in childhood or any history of drug or alcohol abuse.

Endoscopic examination revealed esophageal varices and congestive gastropathy; ultrasound of the liver showed signs of liver cirrhosis with portal hypertension. Laboratory data revealed a low platelet count (83,000; normal value [N.V.] = 150,000-450,000) and leukopenia (3,300; N.V. = 4,000-10,000); transaminases and γ-glutamyl transferase (GGT) serum levels were in the normal range. Serologic markers for antinuclear antibodies (Abs),

anti-smooth muscle Abs, anti-mitochondrial Abs and anti-endoplasmic endothelial Abs were negative. Viral markers revealed a past hepatitis B virus (HBV) infection and the anti-HCV test was negative. Plasma ferritin levels were in the normal range (332 ng/ml; N.V. = 25-380).

Liver biopsy was performed. The histological observation revealed micronodular cirrhosis with focal micro- and macrovesicular steatosis, with scattered glycogenized nuclei, fibrous bridging septa and nodular regeneration, allowing the diagnosis of liver cirrhosis (**Fig. 1A**). At hematoxylin and eosin, eosinophilic bodies were detected in the cytoplasm of periportal and periseptal hepatocytes. On PAS staining after diastase, the globules were intensively PAS-positive and resistant to diastase digestion (**Fig. 1B**). Immunostaining with specific anti-AAT antibodies confirmed AAT storage in the hepatocytes (**Fig. 1C**). In addition, Perls' stain positivity revealed hepatic iron overload (**Fig. 1D**).

Rhodanine and Timm stains for copper were negative. Serum AAT levels were in the normal range (128 mg/dl; N.V. = 100-150 mg/dl) and the immune electro focusing (IEF) pattern did not show any pathological variants. AAT genotype analysis was performed, sequencing exons 2, 3 and 5. The only molecular alteration found was the 51/52Phe deletion in exon 2, in a heterozygous state. The presence of this deletion in one allele was confirmed by using a rapid real-time PCR test specific for the M-Malton mutation [13]. A PCR-restriction fragment length polymorphisms assay, performed for the *HFE* GH gene, showed the absence of the C282Y mutation and the presence of the H63D heterozygous state.

Ten months later, the patient was admitted again to our hospital and insulin-dependent diabetes mellitus was diagnosed. The clinical and laboratory picture of the chronic liver disease was characterized by increased serum levels of GGT and alkaline phosphatase and by increased plasma ferritin levels (661 ng/ml, N.V. = 25-380 ng/ml). The clinical and laboratory picture led to listing the patient for orthotopic liver transplantation.

Two sons, who were apparently healthy, showed a normal AAT genotype on molecular testing, whereas one of them was heterozygous for the H63D GH mutation, in the absence of any clinical or laboratory change from the normal range (**Tab. 1**).

All procedures were approved by the Ethic Human Studies Committee of University Medical Centre of Cagliari (no. Prot. 13/C.E./05), according to the instructions of the Declaration of Helsinki.

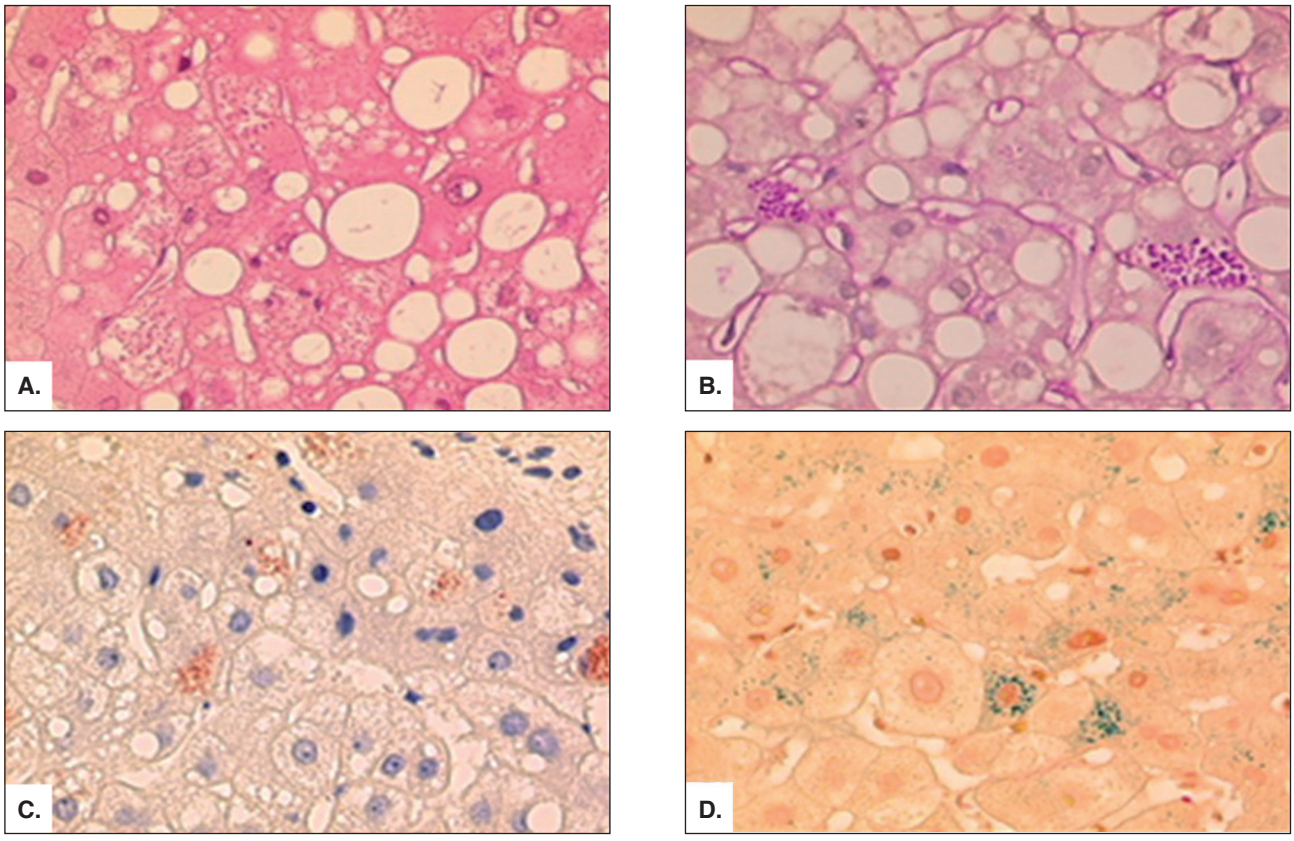

Figure 1. Proband liver biopsy (double heterozigosity for M-Malton and H63D). **A.** Hematoxylin and eosin. **B.** PAS-diastase. **C.** AAT immunohistochemistry. **D.** Perls' stain.

Table 1. Serum alpha-1 antitrypsin (AAT) concentration and AAT and *HFE* genotype of the proband and his children.

	Serum AAT (N.V. = 100-150 mg/dl)	AAT genotype	*HFE* gene	
			C282Y mutation	H63D mutation
Proband	128	M/M-Malton	-/-	-/+
Son 1	136	Normal M/M	-/-	-/+
Son 2	121	Normal M/M	-/-	-/-

AAT: alpha-1 antitrypsin; N.V.: normal value.

Discussion

Genetic disorders associated with metal metabolism form a large group of disorders, mostly associated with defects in protein/enzyme metabolism [14]. Several possibilities can mitigate these metal-related pathological entities and the possible use of novel therapeutic approaches has been proposed in recent years [3].

AATD and GH are two autosomal recessive genetic disorders characterized by increased liver storage of the AAT misfolded protein and iron, respectively.

Only rarely, heterozygosity for these genetic mutations may be associated with inflammation, hepatic fibrosis and with an increased incidence of cirrhosis, depending on a combination of several genetic and epigenetic factors [12].

Since AATD and GH are relatively common in Caucasian populations, a possible relationship between these two metabolic disorders in chronic liver diseases has been considered.

Conflicting data on the concomitant occurrence of AATD and GH have been reported in isolated families and in small groups of patients. Taken together, these data suggest that the presence of the Pi Z allele for AATD associated with GH may contribute to the earlier onset of cirrhosis [12].

The case reported here describes a double heterozygosity of the rare variant M/M-Malton for AATD and the H63D for GH. The molecular data are supported by the concomitant phenotypic expression of both these two disorders in the liver biopsy: the presence of AAT globules inside hepatocytes associated with iron storage in the form of hemosiderin granules. Even if M-Malton is considered a rare pathological variant of AATD, in the Sardinian population this mutation is significantly more frequent than the Z allele [15].

Interestingly, in this island population, the C282Y *HFE* mutation is practically absent, while the H63D mutation is very frequent [16]. Therefore, it is not surprising to find in this population a clinical case of chronic progressive liver disease characterized by the presence of the M-Malton/H63D heterozygosity.

The absence in this patient of viral infection, alcohol abuse, autoimmune markers and other liver agents underlines a real association between M-Malton/H63D and liver diseases.

This possibility was already proposed in another form of AAT/GH heterozygosity, composed by the C282Y and Pi MZ mutations [12].

In these clinical cases, it was suggested that the Z variant of AAT could alter the expression of hepcidin (a crucial player of liver iron metabolism), triggering hepatic iron overload in genetically predisposed individuals, including those heterozygous for H63D [17].

The misfolding protein event present in AATD (peptides involved in conformational diseases have numerous metal binding sites) may in this way be responsible for a possible toxic metal ion homeostasis alteration.

It remains to be clarified if the formation of metal complexes and/or their insoluble aggregates are one cause or a consequence of a possible adaptive mechanism predisposed to control metal overload and/or environmental factors [4].

One possibility is that low levels of circulating AAT could influence the physiological overload of iron normally present in the GH heterozygosity state.

Another possibility is that physiological folding, like glycosylation of AAT protein in the endoplasmic reticulum, might be disturbed by the biological effects induced by an increased amount of transition metal ions like iron.

A third possibility is that iron liver stress, induced by the H63D heterozygosity, may in some way influence the AAT-altered degradation pathway (ubiquitin/proteasome) with a consequent progressive overload of this protein in the liver.

In any case, the resulting liver cell necrosis and inflammation exacerbate the initial pathological phenomenon, leading to a progressive liver fibrosis and cirrhosis. The onset of diabetes in our case could be a possible consequence of another pathological interaction between GH and AATD. In this case, systemic iron overload could be responsible for pan-

creatic cell necrosis in the Langerhans islets [3]. It is important to note that, in order to prevent all these pathological consequences, the use of an iron-chelating therapy or a simple phlebotomy might be determinant [18].

Conclusion

In conclusion, this case report describes the association between two heterozygous states regarding AATD (M-Malton) and GH (H63D), and underlines the importance of the diagnostic role played by the liver biopsy. In fact, the identification of AAT globules inside the hepatocytes, associated with the positivity of Perls' stain and with the normal AAT serum levels and the normal IEF pattern (explained by the hyperactivity of the normal AAT allele during inflammation and by the presence of one M-like variant, M-Malton), is noteworthy.

Due to these complications in the diagnosis, our clinical case confirms the hypothesis that this disease is probably not so rare as reported in the literature, but is rarely diagnosed. It is therefore important for clinicians to be aware of the various clinical circumstances that can cause discordant AAT results. A regular clinical follow-up, already suggested for the Pi MZ heterozygotes, will be determinant also for other rare deficient allelic variants [19, 20].

Declaration of interest

The Authors declare that they have no conflict of interests.

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