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Case report

# Severe steatohepatitis in a patient with a rare neutral lipid storage disorder due to ABDH5 mutation☆

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**Fatty liver disease is mainly caused by alcohol consumption, excessive body weight, dyslipidemia and impaired glucose tolerance, but inherited disorders can sometimes be involved. We report the case of a 40-year-old woman with steatohepatitis and severe portal hypertension, associated with ichthyosis, cataract and hypoacusia. The clinical, pathological and genetic findings were consistent with a diagnosis of Chanarin–Dorfman syndrome (CDS), a rare autosomal recessive inherited neutral lipid storage disorder, and genetic analysis showed that a novel ABHD5 mutation is responsible.**


***Keywords*: Chanarin–Dorfman syndrome; Non-alcoholic steatohepatitis; Ichthyosis**

## 1. Introduction

Fatty liver disease is increasingly common in resource-rich countries. The main causes include alcohol consumption, overweight, and lipid and carbohydrate metabolism disorders, but genetic diseases may sometimes also be involved.

Chanarin–Dorfman syndrome (CDS) is an autosomal recessive genetic disorder of neutral lipid storage that leads to the intracellular accumulation of triacyl glycerols. It is characterised by a clinical phenotype extending from isolated cutaneous manifestations (ichthyosis) to multisystemic involvement (hepatic steatosis, myopathy, cataracts and neurological disease), and mutations in the ABDH5 gene (CGI58, chromosome 3p21.33) [1,2] are involved in its pathogenesis. A laboratory diagnosis of CDS requires the detection of lipid vacuoles in peripheral blood neutrophils (also called Jordan's anomaly) [3,4], and can be confirmed by genetic testing [5,6]. Approximately 40 cases of CDS have so far been reported in peer-reviewed medical journals. Liver enzyme abnormalities and hepatic steatosis are common findings, but severe liver disease has only been described in a few cases.

Herein we describe a case of severe fatty liver disease and hepatic decompensation in a CDS patient bearing a novel ABHD5 mutation.

## 2. Case report

In July 2006, a 40-year-old Italian woman was admitted to a primary care health facility because of variceal

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hemorrhaging with severe anemia (Hb 4.1 g/dl) and, after blood transfusion, fluid restoration and emergency variceal ligation, was transferred to our hospital. She had no history of alcohol or drug exposure, and her family history was not significant. She had suffered from ichthyosis since childhood, and this was confirmed by a physical examination that showed erythroderma with fine scales and palmar and plantar hyperkeratosis. Her body mass index (BMI) was 24.1 kg/m$^2$, and she had no ascites or other physical signs of chronic liver disease.

Table 1 summarises the results of routine laboratory tests. Her aminotransferase values were slightly increased, but her platelet count, bilirubin level and liver synthesis tests were normal. Hepatitis B and C serology was negative. An abdominal ultrasound examination revealed a small liver that was free of focal lesions but with surface nodularity which, in our setting, is a specific sign of cirrhosis [7]. Portal hypertension was confirmed by the dilatation of the portal vein with hepatofugal flow, and severe splenomegaly (longitudinal diameter 16 cm).

Second-line laboratory assessments showed the presence of a low antinuclear antibody (ANA) titre of 1:160 with a speckled pattern, but no other sign of autoimmunity (no evidence of anti-mitochondria, anti-smooth muscle, or liver or kidney microsome antibodies) or anti-transglutaminase antibodies were negative. Her ceruloplasmin, alpha 1-antitrypsin, serum ferritin and tranferrin saturation levels were normal.

**Table 1**
**Laboratory tests at hospital admission**

| Test | Normal value | Patient's value |
|---|---|---|
| Haemoglobin | 12–16 g/dl | 4.1 |
| MCV | 80–97 fl | 78 |
| Platelet count | 150.000–400.000 mm$^{-3}$ | 155.000 |
| Aspartate aminotransferase (AST) | 0–33 U/l | 45 |
| Alanino aminotransferase (ALT) | 0–31 U/l | 37 |
| Gamma glutamyltransferase (GGT) | 0–32 U/l | 32 |
| Bilirubin | <1.2 mg/dl | 1.0 |
| Albumin | 3.4–4.8 g/dl | 3.51 |
| PT ratio | 0.80–1.22 | 1.16 |
| Cholesterol | 100–190 mg/dl | 168 |
| Glicosilated haemoglobin | <4.5 % | <4.5% |
| Immunoglobulin G (IgG) | 9–18 % | 20.5% |
| Ferritin | 10–100 ng/ml | 41 |
| Alpha fetoprotein | <7 ng/ml | 3.3 |
| HBsAg | Negative | Negative |
| Anti-HCV antibody | Negative | Negative |
| Antinuclear antibody (ANA) | Negative | 1:160 specked |
| Anti-smooth muscle (ASMA) | Negative | Negative |
| Ab anti-mitochondria (AMA) | Negative | Negative |
| Liver or kidney microsome antibodies (LKM) | Negative | Negative |
| Alpha 1 antitrypsin | Negative | Negative |
| Ceruloplasmin | Negative | Negative |

Histological examination of a percutaneous liver biopsy sample obtained using an 18 gauge needle documented the presence of diffuse macro and microvesicular steatosis with a subverted architecture and fibrosis (Fig. 1).

Given the absence of common risk factors for fatty liver disease and the severity of the patient's clinical picture, we suspected a complex disease or a rare syndrome. The presence of ichthyosis reminded us of a case report that had appeared in the medical literature a few days earlier [1]; this case had a number of analogies with our own and led us to consider the hypothesis of a lipid storage disorder, particularly CDS. To test this hypothesis, we interviewed the patient further, and carried out some additional laboratory analyses. The patient admitted to having suffered from mild neurosensorial deafness since childhood, and having been diagnosed with bilateral cataracts a few years earlier, and we confirmed these impairments by means of audiometric tests and ophthalmological assessment. In addition, a peripheral blood smear showed Jordan's anomaly (i.e. the presence of lipid vacuoles in peripheral neutrophils), which is regarded as the hallmark of neutral lipid storage disease syndromes (Fig. 2) [3,8]. The patient was therefore discharged from hospital in a stable condition with a clinical diagnosis of CDS, and included an outpatient follow-up programme. Prophylactic therapy with the beta-blocker nadolol at a dose of 80 mg per day, was prescribed.

The diagnosis of CDS was subsequently confirmed by ABHD5 sequencing, which showed a previously unreported homozygous splice-site mutation in intron 1 leading to the alternative splicing of intron 1 pre-mRNA, the retention of intron 1 itself within the mature RNA, and the production of an abnormal protein. Furthermore, the histology was reviewed at a tertiary reference liver pathology centre for metabolic disorders, which formulated a diagnosis of "non-alcoholic steatohepatitis" with "the presence of macrovacuolar steatosis, ballooning hepatocytes, Mallory bodies, inflammatory infiltrate, and pericellular fibrosis, compatible with CDS".

In February 2007, the patient experienced a second episode of variceal hemorrhaging, which was treated by endoscopic variceal ligation and the placement of a transjugular intrahepatic portal systemic shunt (TIPPS). The patient's clinical condition progressively deteriorated due to the presence of portosystemic encephalopathy, a decreasing platelet count (81,000 mm$^{-3}$), increasing bilirubin levels (3.47 mg/dl), and reduced hepatic synthesis (albumin 2.98 g/dl). Her Child-Pugh score was B8, and MELD score 13. She is currently (January 2008) on the waiting list for liver transplantation.

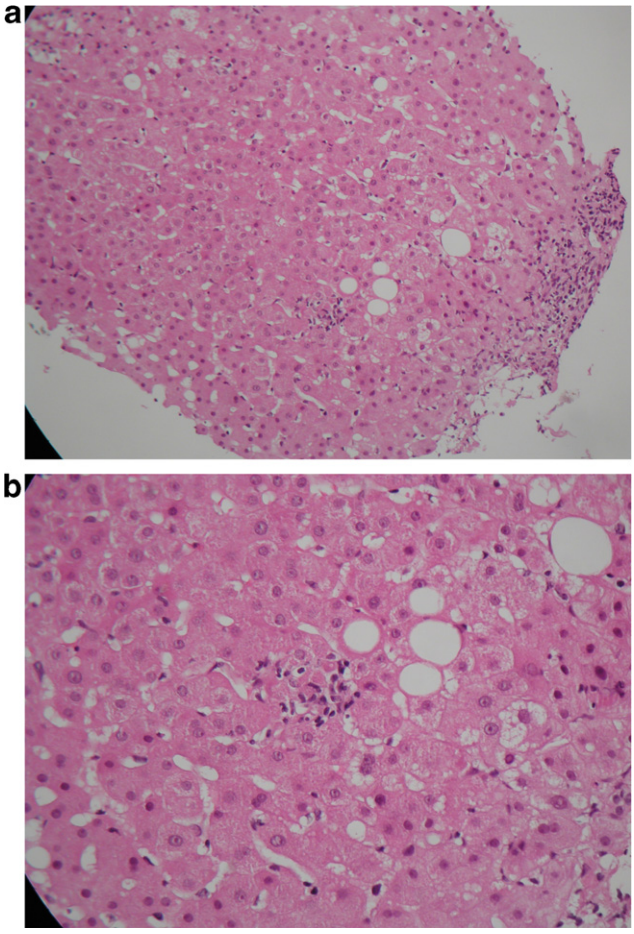


**Fig. 1. E.E. 100× (a), 250× (b). Liver histology documented the presence of diffuse macro and microvesicular steatosis with a mildly subverted architecture and fibrosis, inflammatory infiltrate, ballooning hepatocytes with glycogenate nuclei, and Mallory bodies. [This figure appears in colour on the web.]**

## 3. Discussion

Our patient presented severe portal hypertension and histological evidence of severe steatohepatitis, but was not affected by viral hepatitis and had no common risk factors for alcoholic or non-alcoholic fatty liver disease. This unusual presentation, together with the concomitant presence of a relatively uncommon congenital dermatological manifestation (ichthyosis), guided us towards the diagnosis of CDS, a rare multisystemic disease. Jordan's anomaly (the distinctive laboratory finding for neutral lipid storage disorders) was detected in granulocytes by means of the routine May-Grünwald-Giemsa staining of a blood smear. Routine microscopic examination showed that the droplets were morphologically very similar to those observed in steatotic hepatocytes. As May-Grünwald-Giemsa-negative spots may also be due to cell inclusions not containing neutral lipids or staining artefacts, we used a newly described immunohistochemistry method to confirm the droplets' composition [8]. Genetic analysis confirmed that the patient was affected by an inherited disorder involving the ABHD5 gene. We detected a point mutation of the invariant G of the GT intron 1 donor splice-site giving rise to the truncation of the ABDH5 open reading frame by a premature stop codon, which results in an abnormal protein that is expected to be non-functional as it lacks approximately 96% of amino acid residues.

Approximately 40 patients of CDS have so far been described, only some of whom have undergone genetic testing to identify specific ABHD5 gene mutations [5,6]. We reviewed the original cases of CDS published in peer-reviewed journals [9–16], and found that liver involvement is the second most common clinical manifestation after ichthyosis, with abnormal liver enzyme levels being documented in about 78% of the patients. However, end-stage liver disease has so far been described in only six cases (15%) including our own. Interestingly, most of the patients suffering from hepatic decompensation were more than 40 years old at the time of diagnosis, as compared to a mean age of 19 years among those with little or no hepatic involvement, which suggests that a longer disease duration may favour the onset of hepatic complications. However, as the mutation identified in our patient has never been described before, we cannot exclude the possibility that the severity of her clinical picture was influenced by the type of genetic defect involved.

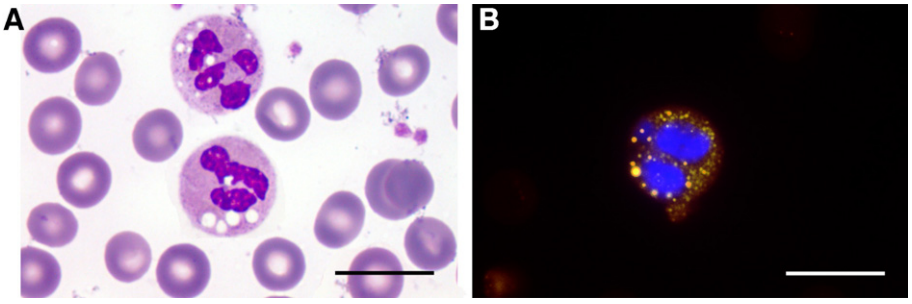


**Fig. 2. Microphotographs of May-Grünwald-Giemsa (A) and Nile red (NR) and DAPI-stained (B) buffy coats showing Jordan's anomaly (the NR fluorescent image has been merged with the corresponding DAPI image). Magnification: 100×. Scale bar: 10 μm. Jordan's anomaly, the most common laboratory finding in CDS patients, is the presence of lipid vacuoles in peripheral leukocytes (neutrophils and eosinophils neutrophils). They predominantly consist of triacyl glycerols or cholesterol esters surrounded by a monolayer of phospholipids and proteins. [This figure appears in colour on the web.]**

This case is also a reminder that steatohepatitis is not always the consequence of unhealthy dietary and drinking habits, but can sometimes be caused by rare genetic syndromes. In addition to neutral lipid storage diseases, other inherited disorders manifesting as severe fatty infiltration of the liver include congenital mitochondriopathies, hypobetalipoproteinemia, choline deficiency, and ornithine transcarbamylase and carnitine palmitoyl transferase deficiencies [1]. Although their frequency is not comparable with that of acquired metabolic fatty liver diseases, their potentially aggressive clinical course means they should not be forgotten.

Finally, our experience highlights the importance of serendipitous events in the diagnosis of rare conditions. Electronic databases can support the insufficient capacity of human minds to retain information, and searching for symptom associations may be helpful but, in the present case, only our regular reading of a medical journal reporting clinical cases allowed us to reach a diagnosis. Case reports may therefore be a direct diagnostic, and are essential for defining the clinical spectrum of rare diseases.

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