Pancreatic exocrine insufficiency: a rare cause of nonalcoholic steatohepatitis

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To the Editor:

It is well known that nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH), is usually associated with obesity and metabolic syndrome. We sometimes encounter NASH patients devoid of obesity, but pathogenesis of obesity-unrelated NASH remains unclear. Here we describe the case of non-obese patient with NASH, which is caused by pancreatic exocrine insufficiency.

A 73-year-old woman was referred because of abnormal liver function tests. She had been in good health, but had been worried about easy fatiguability and weight loss (4 kg in 3 months). She visited her family practitioner, where routine examination revealed mild elevation of serum aminotransferase levels and hepatic steatosis, so she was referred to our facility. She had not taken alcohol or habitual drugs. Her body weight was 45 kg and body mass index was 21.0 kg/m^2. Physical examination showed marked hepatomegaly. Laboratory tests demonstrated mild liver dysfunction: aspartate aminotransferase 96 U/L (normal <38 U/L) and alanine aminotransferase 46 U/L (normal <35 U/L). Serum albumin concentration was decreased (2.8 g/dL; normal 3.8-5.3 g/dL), but her urinalysis and coagulation tests were unremarkable. Viral markers and autoantibodies were negative. An abdominal computed tomography (CT) scan showed massive hepatomegaly and marked decrease in liver parenchyma density (Figure).

Lipid profiles revealed decreased serum total cholesterol concentration (97 mg/dL; normal 130-220 mg/dL). Fasting glucose and insulin concentrations and glycohemoglobin value were normal. Serum ferritin level was elevated (344 ng/mL; normal 3-166 ng/mL), but transferrin saturation rate was normal. Serum ceruloplasmin concentration and urinary copper excretion value were normal, and plasma ammonia and citrulline concentrations were not elevated: her NAFLD was unlikely to be associated with insulin resistance, diabetes, hyperlipidemia, Wilson's disease, or citrin deficiency.[1]

After admission, we noticed her white oily stool. Fecal fat contents were calculated as 39 g/day, indicating the presence of fat malabsorption. Her bentiromide test value was markedly decreased (43%; normal > 73%), and an abdominal CT scan demonstrated marked atrophy of the pancreas without stones or calcification. No abnormalities were found in the gastrointestinal tract by radiologic and endoscopic examinations, and 25 g D-xylose absorption test was normal. Anti-gliadin antibody was negative. Liver biopsy demonstrated diffuse macrovesicular steatosis, ballooning degeneration, glycogenated hepatocyte nuclei, mild lobular inflammation, and perivenular fibrosis (Figure). Based on these findings, the patient was diagnosed as

having NASH, which is possibly caused by maldigestion due to pancreatic exocrine insufficiency. We started oral administration of pancreatic enzymes (Pancreatin^{R} 3 g/day, Toughmac-E^{R} 3 g/day, and Berizym^{R} 3 g/day), which resulted in decreasing steatorrhea, recovery of body weight, and complete normalization of abnormal laboratory test values. In serial CT scan and liver biopsy one year after starting pancreatic enzyme supplementation, hepatomegaly, hepatic steatosis, and histological abnormalities such as ballooning, lobular inflammation, and perivenular fibrosis were markedly improved (Figure), and the patient's health has continued to be much better.

We examined changes in plasma essential fatty acid and amino acid compositions. Although essential fatty acid composition did not change, amino acid composition revealed significant decreases in methionine and tyrosine levels and increase in taurine level, which were normalized one year after starting the treatment.

This case was characterized by non-obesity, weight loss, marked hepatomegaly, and decreases in serum albumin and total cholesterol concentrations, which were distinct from common types of NASH. These clinical features and laboratory test abnormalities, including amino acid composition, were similar to those observed in kwashiorkor,[2] and were improved by pancreatic enzyme supplementation. Protein-energy malnutrition and/or methionine deficiency are supposed to be the etiopathogenesis of NASH in this patient.

Although this type of NASH might be rare, early diagnosis and appropriate treatment can lead to a dramatic improvement. Therefore, in non-obese patients with NAFLD/NASH, clinicians should consider the possibility of latent pancreatic exocrine insufficiency.

References

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Figure. Abdominal CT scan and liver histology before and after pancreatic enzyme supplementation.

An abdominal CT scan showed marked hepatic steatosis and hepatomegaly before treatment. Liver histology examination demonstrated massive macrovesicular steatosis, perivenular fibrosis, ballooned hepatocytes (arrows in lower left panel), glycogenated hepatocyte nuclei, and lobular infiltration of mononuclear cells, which is consistent with the findings of NASH. One year after pancreatic enzyme supplementation, these abnormalities were significantly improved (upper panels of liver histology, Azan-Mallory staining, x40; middle panels, hematoxylin and eosin staining, x200; lower panels, hematoxylin and eosin staining, x400).