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# Rapidly progressive non-alcoholic fatty liver disease due to hypopituitarism. Report of 5 cases

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## Abstract

**BACKGROUND:** A few reports had revealed the clinical associations between hypopituitarism and non-alcoholic fatty liver disease (NAFLD). Further evidences were needed.
**OBJECTIVES:** To report 5 cases of young patients with rapidly progressive NAFLD in conjunction with hypopituitarism, aiming to detect the associations.
**METHODS:** Clinical data of the 5 patients were analyzed retrospectively. All had decompensated liver cirrhosis that was finally attributed to NAFLD. Hypopituitarism was a result of pituitary stalk interruption syndrome in 3 patients and craniopharyngioma in 2.
**RESULTS:** 4 patients were overweight (BMI, 24.2 to 28.4kg/m$^2$). All had insulin resistance (HOMA-IR, 4.8 to 7.2). All suffered from at least one metabolic disorder. All had decompensated liver cirrhosis. The average time duration was 6.9 years between the onset of abnormal liver function and decompensated liver cirrhosis. Fatty liver could be detected in all patients. All had anterior hypopituitarism, and 2 also had posterior pituitary dysfunction. The hormone supplements were insufficient.
**CONCLUSION:** Hypopituitarism may be a rare cause of rapidly progressive NAFLD. Insulin resistance and metabolic disorders caused by multiple hormonal deficiencies may contribute to it. Hormone supplement therapy, especially the growth hormone supplement, should be given at the early age to prevent the severe liver disease.

CASE REPORT

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a liver disease characterized by the histological features of steatosis in the absence of significant alcohol consumption. It comprises a wide spectrum of liver injuries, ranging from simple benign steatosis to steatohepatitis with fibrosis and scarring that can eventually lead to cirrhosis and hepatocellular carcinoma. The definitive diagnosis requires a liver biopsy.

Recently, it has been reported that patients with hypothalamic and pituitary dysfunction are at risk of excessive weight gain, impaired glucose tolerance, dyslipidemia, and may subsequently develop to NAFLD. It is an important but neglected issue that NAFLD in this group of patients progress rapidly, prone to leading to cirrhosis, end-stage liver disease, and even liver-related death.

We presented 5 cases of young patients with decompensated liver cirrhosis of unknown aetiology that was finally attributed to NAFLD associated with hypopituitarism. To the best of our knowledge, the present study contains relatively large sample size, while most of studies in this field are case report.

## MATERIALS AND METHODS

Clinical data of 5 patients with decompensated liver cirrhosis in conjunction with hypopituitarism were analyzed retrospectively.

All of them were admitted to our hospital for decompensated liver cirrhosis with unknown aetiology. Serological testing for hepatitis B and C, cytomegalovirus, and EB virus were all negative. Autoimmune tests were negative for antinuclear antibodies, anti-smooth muscle antibodies, and antimitochondrial antibodies. Iron overload, metabolic liver disorders (Wilson disease, etc) and cholestatic liver disease were all excluded using standard criteria. Drug and alcohol induced were ruled out by history.

3 of them were diagnosed as pituitary stalk interruption syndrome (PSIS) by pituitary MRI. 2 were diagnosed as craniopharyngioma. Both underwent surgical treatment, and 1 also received additional radiotherapy at the hypothalamus-pituitary area.

## RESULTS

*Clinical features*

All of the 5 patients were male. Age at time of diagnosis of decompensated liver cirrhosis ranged from 16 to 30. 4 of 5 patients had a BMI above normal, ranging from 24.2 to 28.4 kg/m$^2$. 3 suffered from pituitary stalk interruption syndrome and 2 craniopharyngioma concomitantly. Time duration between the onset of abnormal liver function and decompensated liver cirrhosis ranged from 0–15 years (average 6.9 years). (Table 1)

**Tab. 1.** Clinical features of 5 cases

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Age (year) | 30 | 26 | 24 | 28 | 16 |
| Gender | male | male | male | male | male |
| Height (cm) | 207 | 180 | 158 | 175 | 175 |
| Weight (kg) | 115 | 85 | 60.5 | 66 | 87 |
| BMI (kg/m$^2$) | 26.8 | 26.2 | 24.2 | 21.6 | 28.4 |
| Concomitant pituitary disease | PSIS | PSIS | PSIS | craniopharyngioma | craniopharyngioma |
| Time duration (year) | 15 | 7 | 0 | 1.5 | 11 |

PSIS: pituitary stalk interruption syndrome

**Tab. 2.** Metabolic status of 5 cases

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| HOMA-IR | 7.2 | 6.5 | 6.1 | 4.8 | 5.9 |
| Hypertension (mmHg) | 125/86 | 120/67 | 103/65 | 110/70 | 112/70 |
| Hyperglycemia | no | no | yes | no | no |
| Hyperlipidemia | yes | yes | yes | yes | yes |
| Hypeluricemia | yes | yes | no | no | no |

*Metabolic status*

All had elevated HOMA-IR and at least one metabolic disorder, including hyperglycemia, hyperlipidemia and hyperuricemia. Hyperlipidemia was the most common metabolic disorder, which can be detected in all patients. (Table 2)

*Liver functions*

Ascites and variceal bleeding were the most common complications of decompensated liver cirrhosis seen in our patients. Aspartate aminotransferase levels were elevated in 4 of 5 patients, whereas alanine aminotransferase levels were elevated in 2 of 5 patients. Bilirubin levels were normal in all except one patient. 3 patients had slightly elevated γ-GT levels. 3 had impaired coagulation function and all had hypersplenism. Imageological examinations showed liver cirrhosis with different degrees of fatty deposits and splenomegaly. Esophagogastroduodenoscopy showed gastroesophageal varices and portal hypertensive gastropathy. Liver biopsy was performed in 3 patients and revealed severe steatosis, mild inflammation and structurally abnormal nodules. (Table 3)

**Tab. 3.** Liver functions of 5 cases

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Ascites | yes | no | yes | yes | yes |
| Variceal bleeding | no | yes | yes | yes | yes |
| Hepatic encephalopathy | no | no | no | no | no |
| ALT (U/L) (5-40) | 33 | 42 | 89 | 10 | 31 |
| AST (U/L) (8-40) | 40 | 66 | 95 | 43 | 90 |
| TBIL (umol/L) (3.4-20.5) | 11.2 | 6.1 | 14.5 | 24.5 | 10.3 |
| DBIL (umol/L) (0-6.8) | 4.1 | 2.8 | 6.5 | 11.8 | 5.0 |
| γ-GT (U/L) (11-50) | 54 | 57 | 47 | 33 | 59 |
| ALB (g/L) (35-55) | 36 | 40 | 41 | 36 | 40 |
| CHE (U/L) (5000-12000) | 2902 | 8673 | 5990 | 2770 | 5319 |
| PT (s) (10.2-14.3) | 16 | 14 | 12 | 18.4 | 14.9 |
| PTA (%) (65-130) | 50.5 | 73 | 89.2 | 41.3 | 55.9 |
| RBC ($\times 10^{12}$/L) (4.09-5.74) | 4.31 | 3.82 | 2.91 | 2.67 | 3.52 |
| WBC ($\times 10^{9}$/L) (3.97-9.15) | 3.51 | 2.89 | 3.84 | 2.63 | 2.13 |
| PLT ($\times 10^{9}$/L) (85-303) | 49 | 63 | 110 | 78 | 48 |
| AFP (ng/ml) (0-10) | 2.22 | 2.87 | 2.23 | 19.66 | 4.28 |
| Ultrasound | liver cirrhosis, splenomegaly, mild fatty liver, massive ascites | liver cirrhosis, splenomegaly, mild fatty liver | liver cirrhosis, splenomegaly, moderate fatty liver | liver cirrhosis, splenomegaly, mild fatty liver, mild ascites | liver cirrhosis, splenomegaly, mild to moderate fatty liver, mild ascites |
| CT | | liver cirrhosis, splenomegaly, mild fatty liver | liver cirrhosis, splenomegaly, moderate fatty liver, mild ascites | liver cirrhosis, splenomegaly, mild fatty liver, mild ascites | liver cirrhosis, splenomegaly, moderate fatty liver, mild ascites |
| MRI | liver cirrhosis, splenomegaly, mild fatty liver, massive ascites, suspicious mass in the left lobe of liver | | | | |
| Esophagogastroduodenoscopy | moderate gastroesophageal varices | severe gastroesophageal varices, moderate portal hypertensive gastropathy | severe gastroesophageal varices, moderate portal hypertensive gastropathy | severe gastroesophageal varices | severe gastroesophageal varices, mild portal hypertensive gastropathy |
| Biopsy | no | yes | yes | no | no |
| Steatosis | | severe | severe | | severe |
| Inflammation | | mild | mild | | mild |
| Fibrosis | | cirrhotic | cirrhotic | | cirrhotic |

*Pituitary functions*

All patients had anterior hypopituitarism, and 2 also had posterior pituitary dysfunction. The hormone supplements were insufficient. Only one patient had ever received growth hormone replacement. (Table 4)

**Tab. 4.** Pituitary functions of 5 cases

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| F (nmol/L) (198.7-797.5) | 91.96 | <25.7 | 66.7 | <25.7 | <25.7 |
| ACTH (pmol/L) (<10.12) | 3.14 | 6.15 | 3.76 | 5.78 | 11.2 |
| FT3 (pmol/L) (4.26-8.1) | 2.74 | 4.0 | 2.97 | 4.24 | 3.42 |
| FT4 (pmol/L) (10.0-28.2) | 7.77 | 5.51 | 6.48 | 5.6 | 7.38 |
| TT3 (nmol/L) (1.49-2.6) | 1.09 | 1.7 | 1.62 | 1.73 | 1.8 |
| TT4 (nmol/L) (71.2-141) | 53.1 | 46.4 | 82.1 | 49.1 | 60.4 |
| TSH (mIU/L) (0.465-4.68) | 7.97 | 6.97 | 1.87 | 5.73 | 3.99 |
| T (nmol/L) (7.66-24.8) | <0.45 | <0.45 | <0.45 | 0.18 | 0.07 |
| LH (mIU/L) (1.37-13.58) | 0.27 | <0.07 | 0.28 | 0.12 | 0.16 |
| FSH (mIU/L) (0.57-12.7) | 0.03 | 0.73 | 0.26 | 0.00 | 0.00 |
| GH (ug/L) (0.06-5.0) | 0.1 | <0.05 | <0.05 | <0.05 | 0.1 |
| IGF-1 (ng/ml) (106-336) | 48 | <25 | <25 | <25 | 41 |
| Posterior pituitary dysfunction | no | no | no | yes | yes |
| Hormone supplement | | | | | |
| Glucocorticoid | no | no | prednisone 5mg/day | had ever | had ever |
| Thyroid hormone | no | no | euthyrox 25ug/day | had ever | euthyrox 62.5ug/day |
| Testosterone | no | had ever | no | had ever | no |
| Growth hormone | no | no | had ever | no | no |
| Vasopressin | | | | yes | yes |

## DISCUSSION

Clinical associations between hypopituitarism and NAFLD had been reported (Hong *et al.* 2011; Bauditz *et al.* 2007). Nakajima *et al.*(Nakajima *et al.* 2005) experienced two cases of pediatric non-alcoholic steatohepatitis (NASH) associated with hypopituitarism. The first patient was diagnosed with a craniopharyngioma at 5 years old and the second as having pituitary dysfunction due to fetal asphyxia at 10 years old. 11 and 8 years later respectively, the two patients were diagnosed as having NASH with liver cirrhosis or advanced fibrosis. Gonzalez Rozas *et al.* (Gonzalez Rozas *et al.* 2016) presented a case of a young patient with liver cirrhosis of unknown aetiology that was finally attributed to panhypopituitarism caused by pituitary stalk interruption syndrome. Jonas *et al.* (Jonas *et al.* 2005) noted the NAFLD in association with panhypopituitarism secondary to a hypothalamic tumor in a 16-year-old boy. After a successful liver transplant the NAFLD recurred very quickly. Fujio *et al.* (Fujio *et al.* 2015) reported a similar case. This is a pediatric patient with NASH associated with hypopituitarism. Twelve months after living donor liver transplantation, abdominal computed tomography showed recurrence of NAFLD. However, most of the studies were case report. Further studies were needed.

The NAFLD in this group of patients seemed to be progressive and severe. In a 21 patients study, patients were diagnosed with NAFLD 6.4±7.5 years after the diagnosis of pituitary/hypothalamic dysfunction. 6 in the 10 patients biopsied had cirrhosis. In the 18 patients following up for 66±33 months, 2 required liver transplantation and 2 died from liver related causes (Adams *et al.* 2004). Our study had similar findings, showing that decompensated liver cirrhosis occurred only 6.9 years after the abnormal liver function being detected.

Insulin resistance is regarded as a hallmark and causal factor of NAFLD (He *et al.* 2016). Insulin resistance favors the mobilization of fatty acids, results in enhanced FFA delivery to the liver, increases de novo hepatic lipogenesis, elevates β-oxidation and oxidative stress, and then leads to apoptosis and consequent liver

damage (Hazlehurst & Tomlinson 2013). In our study, all patients had severe insulin resistance, with HOMA-IR ranging from 4.8 to 7.2.

Patients with hypopituitarism may develop phenotypes similar to metabolic syndrome, including central obesity, hyperlipidemia, hyperglycemia and hyperuricemia. These metabolic changes are principally thought to be due to GH deficiency and reduced insulin-like growth factor-1(IGF-1), although hypothyroidism and hypogonadism have also been implicated. In our study, 4 of 5 patients had a BMI above normal, ranging from 24.2 to 28.4 kg/m$^2$. All the 5 patients had at least one metabolic disorder, with hyperlipidemia being detected in all of them. The main metabolic changes also help to establish a relationship between hypopituitarism and NAFLD.

A three-hit hypothesis has been proposed as the pathogenesis underpinning NAFLD. The three-hit was defined as firstly the accumulation of lipid, then initiation of an inflammatory response, and finally emergence of defective repair and regenerative response. Hypopituitarism with multiple hormonal deficiencies, elevating insulin resistance and relevant metabolic disorders, may contribute to the occurrence of any of the three possible underlying mechanisms. In some instances, correction of these defects has been shown to have a beneficial impact.

GH functions as a major metabolic hormone in adults. It promotes fat metabolism and enhances the low-density lipoprotein clearance, regulates glucose metabolism both directly and by antagonizing insulin action, reduces protein oxidation and stimulates proteins synthesis (Takahashi 2012). The level of insulin resistance is higher in patients with GH deficiency. Circulating IGF-I is derived predominantly from hepatocyte by the stimulation of GH. Reduction in IGF-1 secretion would lead to increased hepatic glucose production and favour peripheral insulin resistance. Both GH and IGF-1 are believed to be important in the regulation of hepatic lipid metabolism (Takahashi 2012). Given the fact that GH secretion is most frequently impaired in patients with hypothalamic-pituitary organic disease, it is speculated that NAFLD is attributable to GH deficiency. A case report noted improvements in fatty liver associated with panhypopituitarism not with hydrocortisone or levothyroxine treatment, but with growth hormone administration, suggesting that fatty liver is at least partly attributable to GH deficiency (Takano *et al.* 1997). A large cross-sectional study including 1667 subjects diagnosed as NAFLD and 5479 controls showed a significant association between lower serum GH levels and NAFLD (Xu *et al.* 2012). Reduced IGF-I levels are also detected in subjects with NAFLD (Arturi *et al.* 2011). The exact mechanisms are not fully understood. GH replacement therapy can significantly reduce serum liver enzyme concentration, reduce the fibrotic marker concentrations and improve the histological changes in the liver in patients with NASH (Nishizawa *et al.* 2012; Takahashi *et al.* 2007; Fujio *et al.* 2015). Meanwhile, treatment with IGF-1 seems to reverse fibrotic effects and is the other possible therapeutic option (de la Garza *et al.* 2017).

Thyroid hormones play a key role in the regulation of metabolism. Recent study has shown the importance of thyroid hormones for the intrahepatic metabolism of lipids, by stimulating the fatty acid β-oxidation and inducting of hepatic autophagy to deliver fatty acids to mitochondria (Sinha *et al.* 2012). It is found in a cross-sectional study that overt hypothyroidism has been associated with the development of NAFLD (Ittermann *et al.* 2012). Subjects with hypothyroidism were 2.1 and 3.8 times more likely to have NAFLD and NASH respectively, showing in a cohort of 246 patients with biopsy-proven NAFLD and 430 age-, gender-, race- and BMI-matched control subjects (Pagadala *et al.* 2012). Pharmacological correction of hypothyroidism is metabolically beneficial and can improve lipid profile and hepatic steatosis, as measured by magnetic resonance spectroscopy (Gardner *et al.* 2011).

Studies have established a relationship between a low serum testosterone level and the onset of NAFLD. In a retrospective cross-sectional study, when patients were divided into quintiles according to serum testosterone, men in the low serum testosterone quintile were at a higher risk for NAFLD than in the highest serum testosterone quintile (OR 5.12) (Kim *et al.* 2012). Furthermore, an inverse correlation between serum testosterone and BMI/waist circumference was detected (Gapstur *et al.* 2002). Testosterone replacement in hypogonadal men significantly reduces factors closely related to the start of NAFLD, including the weight, BMI, waist circumference, leptin, insulin and circulating TNFa (Kalinchenko *et al.* 2010). It is found that testosterone therapy can decrease the liver fat accumulation measured by CT scan (Hoyos *et al.* 2012).

Growing evidence has revealed the associations between hypopituitarism and rapidly progressive non-alcoholic fatty liver disease. This is a condition that has been overlooked, and would be useful both for hepatologists and endocrinologists. We reported here 5 patients with NAFLD associated with hypopituitarism to strengthen the evidence. Further investigations are necessary to clarify the precise mechanisms and the management of the disease.

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## CONFLICT OF INTEREST

The authors declared no conflict of interest.

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