Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis in Patients with Childhood-Onset Adult Growth Hormone Deficiency

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Abstract. Patients with growth hormone deficiency (GHD) often have obesity, hyperlipidemia, fatty liver and diabetes mellitus which are similar to metabolic syndrome. Recently, it has been reported that non-alcoholic fatty liver disease (NAFLD), especially with non-alcoholic steatohepatits (NASH) are associated with metabolic syndrome. Therefore, it is interesting to know the relationship between GHD and NASH/NAFLD. In the present study, we investigated NASH/NAFLD in patients with childhood-onset adult GHD. A retrospective chart analysis was performed on 38 patients (M/F 19/19, age 35 ± 11, range 18–62) with childhood-onset GHD who visited our outpatient clinic. Clinical course, symptoms and laboratory data were reviewed in these patients. The average body mass index (BMI) and the value of HOMA-R of the patients were 24.9 ± 3.8 kg/m² and 3.09 ± 2.9, respectively. Liver dysfunction was found in 17 patients. We performed abdominal ultrasonography on 7 of 17 patients with liver dysfunction, and observed fatty liver change in all patients. The majority of these patients had impaired glucose tolerance and dyslipidemia by the time of diagnosis of NAFLD. Moreover, microscopic examination of liver biopsy specimens from one patient revealed NASH with fibrosis. In conclusion, patients with GHD are at risk of excessive weight gain, impaired glucose tolerance, and dyslipidemia with subsequent development of NAFLD. As NAFLD is related to the occurrence of NASH and cirrhosis, this novel evidence that GHD may be accompanied by progressive NAFLD has important implications for follow-up and management of patients with GHD.

Key words: NAFLD, NASH, COGHD

Introduction

Patients with growth hormone deficiency (GHD) often have obesity, hyperlipidemia and insulin resistance which are similar to metabolic syndrome (1). The pathophysiological roles of GH on fatty liver in these patients have not been fully investigated. Recently, it has been reported that non-alcoholic fatty liver disease (NAFLD), especially with non-alcoholic steatohepatitis (NASH) are associated with metabolic syndrome (2). NASH is a liver disease characterized by the histological features of steatohepatitis in the absence of significant consumption. Therefore, it is interesting to know the relationship between
GHD and NASH/NAFLD. In the present study, we investigated NASH/NAFLD in patients with childhood-onset adult GHD, and report a case with non-alcoholic steatohepatitis.

Patients and Methods

A retrospective chart analysis was performed on 38 patients with childhood-onset GHD (male/female 19/19, age 35 ± 11 yr, range 18–62 yr), who visit our clinic. Clinical course, symptoms and laboratory data were reviewed in these patients. We looked for the presence of hepatic steatosis using ultrasonography in a study of 7 patients. We also performed a liver biopsy on one patient with childhood-onset GHD. Patients positive for hepatitis B or C serology or with evidence of inherited, autoimmune, drug-induced, or metabolic liver disease were excluded using standard clinical, laboratory, imaging and histologic criteria. In addition, patients with weekly alcohol intake of more than 140 g were excluded. Diagnosis of NAFLD was determined by liver biopsy or fatty infiltration on imaging studies in association with abnormal liver transaminase. Patients were excluded if they had a secondary cause of NASH such as Cushing’s syndrome or drugs etc. The beginning of pituitary dysfunction was taken from a date of brain surgery if applicable, or time of clinical diagnosis. Time of diagnosis of NAFLD was taken from date of clinical diagnosis if the patient was not biopsied, or the date of liver biopsy. Body mass index (BMI), transaminase, and lipid and glucose profiles were obtained at time of diagnosis of the pituitary disease and at regular intervals thereafter.

Results

The average body mass index (BMI) and the value of HOMA-R in patients with childhood-onset GHD were 24.9 ± 3.8 kg/m² and 3.09 ± 2.9, respectively. Liver dysfunction was found in 17 of 38 patients. Their transaminase levels are shown in Fig. 1. Different from alcoholic liver dysfunction, serum alanine aminotransferase (ALT) predominance is observed in NASH. Therefore, the serum asparatate aminotransferase (AST)/ALT ratio is useful for differential diagnosis between alcoholic liver dysfunction and NASH. The AST/ALT ratio was less than one in most NASH patients.

The incidence of liver dysfunction in patients with childhood-onset GHD is shown in Fig. 2. AST was normal in 68%, while it was slightly increased in 32% of the patients. ALT was normal in 58%, while it was slightly increased in 37%, and elevated over 100 IU/ml in 5% of the patients.

We performed abdominal ultrasonography on 7 of 17 patients with liver dysfunction, and observed fatty liver change in all patients. The majority of these patients had impaired glucose tolerance and dyslipidemia by the time of
diagnosis of NAFLD. A liver biopsy was performed on one patient. Histologic features of the liver observed were macrovesicular steatosis, pericellular and centrilobular fibrosis, and ballooned hepatocytes (Fig. 3). We diagnosed NASH from these findings.

**Discussion**

The clinical association between features of metabolic syndrome (obesity, diabetes and hyperlipidemia) and NAFLD was noted in the first descriptions of the disease (2). It has been shown subsequently that NAFLD is intimately related to insulin resistance (3–5). The metabolic changes that accompany hypopituitarism are truncal obesity, hyperlipidemia and insulin resistance. These metabolic changes are principally thought to be due to GH deficiency, although altered cortisol and gonadotropin-sex steroid metabolism have also been implicated (1, 6, 7).

Patients with hypopituitarism associated with GH deficiency have fatty infiltration of the liver more frequently than patients with anterior pituitary hormone deficiency without GH deficiency (8). In addition, patients with NAFLD have lower GH levels compared with control subjects (9), although this may simply reflect the decrease in GH that occurs with obesity (10).

In conclusion, patients with GHD are at risk of excessive weight gain, impaired glucose tolerance, and dyslipidemia with subsequent development of NAFLD that is related to the occurrence of NASH and cirrhosis. This novel evidence that GHD may be accompanied by progressive NAFLD has important implications for the follow-up and management of patients with GHD.

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**References**


