

# Nonalcoholic Fatty Liver Disease Among Patients With Hypothalamic and Pituitary Dysfunction

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Patients with hypopituitarism develop a phenotype similar to metabolic syndrome with central obesity and diabetes. Similarly, patients with hypothalamic damage may develop central obesity, insulin resistance, and hyperphagia. We sought to examine the clinical associations between hypopituitarism, hypothalamic dysfunction, and nonalcoholic fatty liver disease (NAFLD). A case series of patients seen at our institution with diagnoses of hypopituitarism, hypothalamic obesity, or craniopharyngioma and NAFLD was undertaken. Clinical, laboratory, and liver biopsy features were reviewed. Twenty-one patients were identified. NAFLD was diagnosed  $6.4 \pm 7.5$  years (median 3 years) after the diagnosis of hypothalamic/pituitary dysfunction. Mean gain in body mass index (BMI) between diagnoses of hypothalamic/pituitary disease and NAFLD was  $11.3 \pm 8.9$  kg/m<sup>2</sup> at an average yearly rate of  $2.2 \pm 2.2$  kg/m<sup>2</sup>. The majority of patients developed elevated glucose levels and dyslipidemia by time of diagnosis of NAFLD. Of the 10 patients biopsied, six were cirrhotic, two had nonalcoholic steatohepatitis (NASH) with fibrosis, and two had simple steatosis. Long-term follow-up of  $66 \pm 33$  months (range 12–120) was available for 18 patients. Two required liver transplantation. Six patients died, two from liver related causes. In conclusion, patients with hypothalamic and/or pituitary disease are at risk of excessive weight gain, impaired glucose tolerance, and dyslipidemia with subsequent development of NAFLD. This group has a high prevalence of cirrhosis placing them at risk for liver-related death. The novel evidence that hypothalamic/pituitary dysfunction may be accompanied by progressive NAFLD has important implications for the work-up and management of patients with hypothalamic/pituitary disease. (HEPATOLOGY 2004;39:909–914.)

It has been known for several decades that experimental obesity produced by hypothalamic injury in various species of animals is uniformly accompanied with liver damage, progressing occasionally to cirrhosis.<sup>1</sup> Severe obesity is also observed in patients with hypothalamic dysfunction due to structural lesions (*e.g.*, craniopharyngioma) or genetic lesions (*e.g.*, Prader-Willi syndrome).<sup>2</sup> It is proposed that the damaged or dysfunctional hypothalamus in these patients is insensitive to the effect of leptin, an anorectic hormone produced mostly by adipose tissue.<sup>3</sup> A similar phenotype is observed in *fa/fa* (Zucker) rats and *db/db* mice, which are leptin-resistant because of

mutations of the leptin receptor; this phenotype is also seen in leptin-deficient *ob/ob* mice.<sup>4</sup> These animal models develop obesity, insulin resistance, and fatty liver. Patients with nonalcoholic fatty liver disease (NAFLD) are generally insulin resistant and typically display clinical features of central obesity and impaired glucose tolerance.<sup>5–7</sup> Patients with hypopituitarism and resultant growth hormone (GH) deficiency develop a similar phenotype of obesity and insulin resistance.<sup>8</sup>

Because of the similar clinical phenotypes of obesity and insulin resistance in patients with hypopituitarism and hypothalamic dysfunction, we hypothesized that these patients would be prone to developing NAFLD. To our knowledge, only two cases (one in German) have been reported.<sup>9,10</sup> Therefore, we sought to examine in this longitudinal cohort study the clinical association between hypopituitarism, hypothalamic dysfunction and NAFLD, as well as to determine the long-term outcome of these patients.

## Materials and Methods

### Patient Population

Patients with a diagnosis of either panhypopituitarism, hypothalamic obesity, or craniopharyngioma in conjunc-

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; NASH, nonalcoholic steatohepatitis; GH, growth hormone.

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tion with a diagnosis of NAFLD were identified. These patients were seen at our institution between January 1990 and December 2001 and were identified using our computerized master diagnostic index. This database consists of diagnoses imputed by treating physicians of all patients visiting the institution. Patients with positive hepatitis B or C serology or with evidence of inherited, autoimmune, cholestatic, drug-induced, or metabolic liver disease were excluded using standard clinical, laboratory, imaging, and histologic criteria. In addition, patients with a weekly alcohol intake of 140 g or more were excluded. Diagnosis of NAFLD was determined by liver biopsy or by fatty infiltration on imaging studies in association with abnormal liver enzymes. Patients were excluded if they had a secondary cause of NAFLD.

During the 12-year study period, a total of 945 patients with a diagnosis of panhypopituitarism, hypothalamic obesity, or craniopharyngioma were seen at our institution. Liver enzymes were not measured in 66 (7%) patients, leaving a total of 879 patients for evaluation. Twenty-seven patients were initially identified, but six were excluded because of the presence of liver disease other than primary NAFLD (one with alcoholic liver disease, one with drug-induced liver disease) or the absence of confirmed NAFLD (two had normal liver ultrasounds, two had not had liver imaging). Twenty-one out of the 879 (2.3%) patients comprised our patient population.

Time of diagnosis of pituitary or hypothalamic dysfunction was taken from date of brain surgery if applicable, or time of clinical diagnosis. Time of diagnosis of NAFLD was taken from date of liver biopsy or date of clinical diagnosis if the patient was not biopsied. Body mass index (BMI), liver enzymes, and lipid and glucose profiles were obtained at time of diagnosis of the pituitary/hypothalamic disease and at regular intervals thereafter. Liver histology was reviewed by liver pathologists and was staged and graded according to the classification published by Brunt and colleagues.<sup>11</sup> Patient follow-up was extended to May 2003.

Continuous data are presented as mean  $\pm$  SD, and frequency data are presented as the number (proportion) of patients with a condition. The study was approved by the Mayo Institutional Review Board, and all patients or responsible guardians gave informed consent for participation in medical research.

## Results

Of the 21 patients, 14 were female, 19 were Caucasian, and two were Hispanic. Mean age at time of diagnosis of pituitary/hypothalamic disease was  $30 \pm 20$  years (range 3–66). Mean age at time of diagnosis of NAFLD was  $36 \pm 22$  years (range 9–78).

### *Pituitary/Hypothalamic Disease*

Brain tumor was the most common cause of hypothalamic/pituitary dysfunction; it affected 15 patients, including eight with craniopharyngioma, six with pituitary adenoma, and one with astrocytoma. The remaining six patients had idiopathic hypopituitarism (four patients), hypophysitis (one patient), and Prader-Willi syndrome (one patient). All patients with tumors underwent surgery and four received additional radiotherapy. All patients were receiving physiologic doses of glucocorticoid and thyroxine replacement, apart from two who were on sex hormone replacement only. Nine patients were on vasopressin supplement. Growth hormone deficiency was tested in nine patients and confirmed in seven. Hyperphagia was present in five patients.

### *Association With Metabolic Syndrome*

**Body Mass Index.** Serial BMI measurements from time of diagnosis of pituitary/hypothalamic disease were available in eleven patients. Ten of these eleven patients gained weight. The average gain in BMI between diagnoses of pituitary/hypothalamic disease and NAFLD was  $11.3 \pm 8.9$  kg/m<sup>2</sup> at an average yearly rate of  $2.2 \pm 2.2$  kg/m<sup>2</sup>. Serial weights were not available for the remaining 10 patients, although one patient was noted to have a marked weight gain after removal of their craniopharyngioma, with a subsequent BMI recording of 35.3 kg/m<sup>2</sup>.

At time of diagnosis of NAFLD, 18 of 21 patients had a BMI above normal. Five patients were overweight (BMI 25.1–29.9 kg/m<sup>2</sup>), 13 were obese (BMI  $\geq 30$  kg/m<sup>2</sup>) with four of these being severely obese (BMI  $> 40$  kg/m<sup>2</sup>).

**Glucose Tolerance.** Fasting blood glucose levels at time of diagnosis of pituitary/hypothalamic disease were elevated in only one patient who was diabetic. Subsequently, eight patients had elevated glucose levels, including six with overt diabetes (glucose  $\geq 126$  mg/dL) and two with glucose intolerance ( $\geq 110$  mg/dL). At time of diagnosis of NAFLD, fasting blood glucose was elevated in 13 (62%) of 21 patients, including 10 with diabetes and three with glucose intolerance.

**Dyslipidemia and Hypertension.** Fasting triglyceride and cholesterol levels increased after diagnosis of pituitary/hypothalamic disease as shown in Fig. 1A and 1B, respectively. At time of diagnosis of NAFLD, 14 patients (67%) had hypertriglyceridemia ( $>150$  mg/dL), eleven (52%) had low HDL levels ( $<40$  mg/dL for females,  $<50$  mg/dL for males) and seven (33%) patients had hypercholesterolemia ( $>240$  mg/dL). At time of diagnosis of NAFLD, five patients were hypertensive. Two of these were diagnosed after their pituitary/hypothalamic disease was detected.

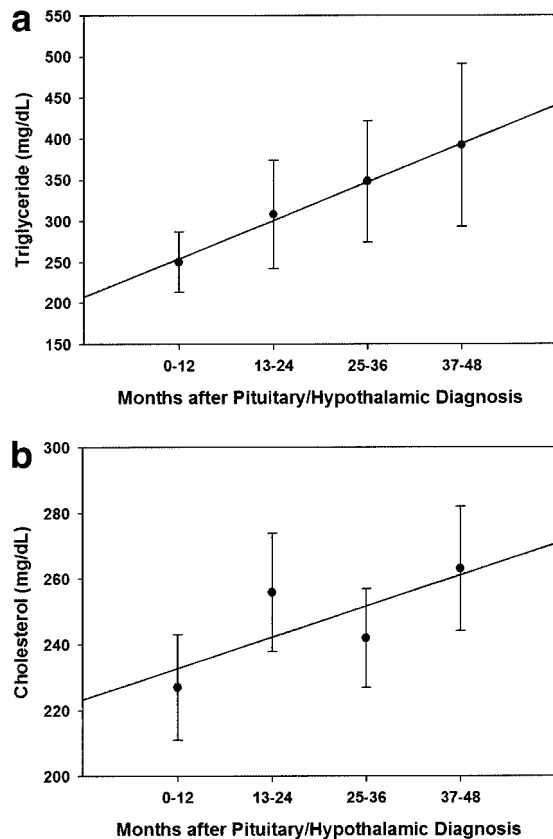


Fig. 1. Mean levels of (A) triglyceride and (B) cholesterol in the first 48 months after diagnosis of pituitary/hypothalamic disease. Regression line and standard error bars are shown.

***Acanthosis Nigricans.*** Three patients had acanthosis nigricans at time of diagnosis of their NAFLD. Two of these patients had craniopharyngiomas removed at ages 8 and 12 with subsequent diagnoses of NAFLD at ages 12 and 26 years, respectively. The third patient had Prader-Willi syndrome with NAFLD diagnosed at age 20.

#### ***Association With NAFLD and Follow-up***

The 21 patients were diagnosed with NAFLD  $6.4 \pm 7.5$  years (median 3 years) after the diagnosis of pituitary/hypothalamic dysfunction. Liver enzymes were available and within the normal range in six patients at time of diagnosis of pituitary/hypothalamic disease. All patients subsequently developed abnormal liver enzymes by time of diagnosis of NAFLD (Table 1). Aspartate aminotransferase was elevated in all patients, whereas alanine aminotransferase was elevated in 13 of 17 (76%) patients. Five patients had elevated alkaline phosphatase levels for their age and gender, including four patients with less than twice (1.3, 1.3, 1.5, and 1.8) the upper limit of normal and one patient with more than twice (2.7) the upper limit of normal. Imaging studies of the abdomen ruled out bile duct disease in the 21 patients. Furthermore, the

patient who had alkaline phosphatase levels 2.7 times that of normal eventually underwent liver transplantation with the explant liver showing cirrhosis with no features of bile duct disease or cholestatic liver disease.

In 10 patients, the diagnosis of NAFLD was confirmed by liver biopsy; six patients were cirrhotic (29% of total cohort), two had nonalcoholic steatohepatitis (NASH) with fibrosis, and two had simple steatosis. Histologic features of these patients are summarized in Table 2.

Long-term follow-up after diagnosis of NAFLD was  $66 \pm 33$  months (range 12–120) and was available for 18 patients; the other three were lost to follow-up. Two patients underwent liver transplantation. One of these underwent transplantation at age 25 after being diagnosed with idiopathic anterior pituitary failure at age 16. The second patient underwent transplantation at age 46 after having a craniopharyngioma removed at age 10.

Overall, six patients (29%) died. Two deaths were liver-related and occurred in cirrhotic patients. One died from hepatocellular carcinoma, and the other died after liver transplantation from recurrent NASH and hepatopulmonary syndrome. One other cirrhotic patient died from a bleeding gastric ulcer. Two patients with simple steatosis died from non-liver-related causes (one from lymphoma and one from a bleeding Dieulafoy lesion). One patient died from peritonitis that was unrelated to their liver disease.

## **Discussion**

The clinical association between features of insulin resistance (metabolic) syndrome (obesity, diabetes, and hyperlipidemia) and NAFLD was noted in the first descriptions of the disease.<sup>12</sup> It has been shown subsequently that NAFLD is intimately related to insulin resistance.<sup>5–7</sup> Other conditions associated with insulin resistance, such as hypertension, hyperuricemia, lipodystrophy and polycystic ovarian disease, have also been described in association with NAFLD.<sup>13</sup> With this series, we are expanding the clinical association to include patients with hypopituitarism and hypothalamic dysfunction. In these patients, central pituitary/hypothalamic disease tended to occur at a relatively young age. The resultant hormonal dysfunction was followed by precipitous weight gain and the development of hyperglycemia, dyslipidemia, and NAFLD. NAFLD developed relatively quickly (average 6.4 years) after the diagnosis of pituitary/hypothalamic dysfunction, and liver disease in these patients was severe; 60% of those biopsied had cirrhosis, and 14.3% (three) of the 21 were either transplanted or died from liver-related causes during follow-up. Similarly, two case reports have described the development of NASH

**Table 1. Characteristics of the Patient Population: Liver Enzymes at Time of Diagnosis of NAFLD (n = 21)**

Patient No.	Sex	Age at Diagnosis of Hypothalamic/Pituitary Disease (y)	Years Between Diagnoses	Alanine Aminotransferase (Times Upper Normal)	Aspartate Aminotransferase (Times Upper Normal)	Alkaline Phosphatase (Times Upper Normal)	Bilirubin (mg/dL)	Albumin (g/dL)	Prothrombin Time (seconds)
1	M	34	1	4.6	2.7	0.9	0.9	4.1	9.8
2	F	54	10	0.7	1.2	0.6	0.9	3.9	11.9
3	F	18	12	NA	2.0	1.8	0.3	4.3	12.6
4	M	58	16	0.8	1.8	1.3	0.8	4.1	NA
5	F	66	12	NA	5.3	0.6	0.8	NA	12.5
6	F	42	9	1.3	1.4	0.8	0.3	3.5	12.9
7	M	53	4	NA	2.7	0.7	0.3	4.4	NA
8	F	43	0	2.7	1.7	0.8	0.4	4.7	9.4
9	F	15	0	5.8	5.5	0.6	0.5	4.7	9.5
10	M	8	2	2.3	2.1	0.8	0.2	4.2	9.8
11	F	37	0	1.0	2.8	0.4	0.9	4.2	NA
12	M	15	2	1.9	1.8	1.3	0.4	4.7	10.5
13	F	52	3	2.0	1.4	0.6	0.4	4.3	NA
14	F	16	8	0.9	1.3	1.0	1.2	4.1	14.4
15	M	50	0	1.6	1.5	0.5	0.4	3.8	NA
16	F	6	3	NA	5.4	0.9	0.6	4.2	NA
17	F	10	32	1.1	2.2	2.7	0.9	3.2	12.1
18	F	5	7	3.1	2.0	0.4	0.6	4.8	11.8
19	M	27	0	1.7	10.6	1.5	0.5	4	10
20	F	14	2	2.9	2.1	0.6	0.3	3.8	10
21	F	3	11	1.6	2.6	1.0	0.2	4.5	11
Mean ± SD		30 ± 20	6.4 ± 7.5	2.1 ± 1.3	2.9 ± 2.2	0.9 ± 0.5	0.6 ± 0.3	4.2 ± 0.4	11.2 ± 1.5

NOTE: The normal range for aspartate aminotransferase is 12-31 U/L; alanine aminotransferase, 9-29 U/L for females and 10-45 U/L for males; total bilirubin, 0.1-1.0 mg/dL; albumin, 3.5-5.0 g/dL; prothrombin time, 8.4-12 seconds. The normal range for alkaline phosphatase activity in our institution varies according to age and gender. The upper limit of normal of alkaline phosphatase ranges from 213-1055 U/L for a population with the same age and gender distribution as our 21 cases. Abbreviations: M, male; F, female; NA, not available.

cirrhosis in two children with panhypopituitarism, one of whom subsequently died at age 13.<sup>9,10</sup>

The metabolic changes that accompany hypopituitarism are central obesity, hyperlipidemia, and insulin resistance. These metabolic changes are principally thought to be due to GH deficiency, although altered insulin-like growth factor-1, cortisol, and gonadotropin metabolism have also been implicated.<sup>8,14,15</sup> Adult patients with anterior pituitary deficiency and associated GH deficiency have fatty infiltration of the liver more frequently than patients with anterior pituitary hormone deficiency without GH deficiency.<sup>16</sup> In addition, patients with NAFLD have lower GH levels compared with unmatched controls,<sup>17</sup> although this may simply reflect the decrease in GH that occurs with obesity.<sup>18</sup> Furthermore, it is not clear

that the level of insulin resistance in GH-deficient patients is greater than in BMI-matched healthy controls.<sup>8,19-21</sup> This suggests that obesity may play a more important role in the development of insulin resistance than GH deficiency *per se*. To confuse the issue further, acromegaly and GH excess are associated with diabetes mellitus.<sup>22</sup> Similarly, GH supplementation in deficient patients can worsen insulin resistance and increase lipolysis, leading to increased free fatty acid concentrations.<sup>14,23</sup> These metabolic changes would presumably instigate or worsen NALFD.

Although the role of growth hormone and insulin sensitivity independent of obesity is unclear, recent reports have focused on the role of leptin. Leptin levels are significantly increased among patients with hypopituitarism and GH deficiency compared with BMI and body fat content-matched controls.<sup>20,24</sup> Presumably this reflects enhanced peripheral and/or central resistance to leptin. Similarly, hyperleptinemia that is out of proportion to the level of obesity occurs in patients with hypothalamic damage post-craniopharyngioma resection, suggesting central leptin resistance.<sup>3</sup>

Resistance to leptin has been modeled in the *fa/fa* (Zucker) rat and the *db/db* mouse, both of which have defective leptin receptors. Hypothalamic resistance to leptin may decrease inhibition of orexigenic hormones such as neuropeptide Y and Agouti-related peptide, leading to net increase in fat mass, hyperinsulinemia and a decrease in metabolic rate.<sup>25</sup> The resultant phenotype in these animals is one of hyperphagia, obesity, insulin resistance,

**Table 2. Histological Findings on Liver Biopsy (n = 10)**

Patient No.	Steatosis	Inflammation	Fibrosis
1	Mild	Mild	Portal
2	Severe	Moderate	Cirrhotic
5	Severe	Nil	Nil
6	Nil	Nil	Cirrhotic
8	Mild	Nil	Nil
12	Mild	Moderate	Cirrhotic
14	Severe	Mild	Cirrhotic
17	Nil	Nil	Cirrhotic
18	Mild	Mild	Cirrhotic
20	Severe	Nil	Pericellular and Portal

NOTE: Patient numbers corresponds to patient numbers in Table 1. Patient 6 was diagnosed with cirrhosis post mortem and was clinically thought to have burnt-out NASH. Patient 17 was clinically thought to have burnt out NASH; pathology specimen was her explanted liver.

and NAFLD.<sup>4</sup> At least five of our patients shared this phenotype of hypothalamic obesity with hyperphagia and marked obesity. However, hyperphagia is not always present in this syndrome,<sup>2,26</sup> and it is probable that more of our patients suffered from hypothalamic obesity.

Besides having a role in mediating obesity and subsequent insulin resistance in these patients, leptin resistance/hyperleptinemia may also have a role in the genesis of advanced NAFLD. Leptin has pro-inflammatory effects and has been implicated in enhancing adipocyte production of tumor necrosis factor  $\alpha$ .<sup>27,28</sup> Tumor necrosis factor  $\alpha$  is hepatotoxic and promotes insulin resistance. In addition, leptin has been characterized as a pro-fibrotic cytokine in animal models of liver fibrosis and fatty liver,<sup>29,30</sup> and in human NAFLD leptin levels correlate with severity of liver fibrosis independently of BMI and degree of insulin resistance.<sup>31</sup>

There are other potential explanations for NAFLD in these patients. All patients except two were on corticosteroid replacement, which is a known cause of liver steatosis. However, it is rare for corticosteroid-induced steatosis to progress to steatohepatitis and cirrhosis, as was observed frequently in our patients.<sup>32</sup> Furthermore, the dosing of corticosteroid used in our patients was physiologic, replacing absent endogenous corticoids. Thus it is unlikely this physiologic dosage of corticosteroids had a significant role in the development and progression of NAFLD in our patients.

One weakness of our series is that we did not measure the degree of insulin resistance and levels of adipocyte hormones (*e.g.*, leptin, adiponectin) at the time of diagnosis of hypothalamic/pituitary dysfunction and subsequently thereafter. Thus we are describing here only the association (instead of causation) of NAFLD and hypothalamic/pituitary dysfunction. In addition, because this is a retrospective study, a degree of selection and ascertainment bias cannot be completely ruled out. For instance, liver enzymes were measured only once in many patients with hypothalamic/pituitary dysfunction, and their normality does not completely exclude the presence of NAFLD. Thus it is likely that the 2.3% (21/879) prevalence of NAFLD reported in this study is an underestimate of the real prevalence of the disease. Further prospective studies with a more detailed metabolic/hormonal evaluation of these patients would better characterize the pathogenesis and prevalence of NAFLD among patients with hypothalamic/pituitary dysfunction. Despite these limitations, however, we believe our data provide important implications for the work-up and management of patients with hypothalamic/pituitary dysfunction. The novel evidence that hypothalamic/pituitary dysfunction may be accompanied by progressive

NAFLD would be useful both for hepatologists and endocrinologists.

## Conclusions

We have identified a set of patients with pituitary and/or hypothalamic disease who developed obesity, features of insulin resistance, and NAFLD. NAFLD developed rapidly after pituitary/hypothalamic dysfunction, and the morbidity and mortality associated with their liver disease was severe. Further investigations in these patients may offer some unique insights into the pathogenesis and the role of leptin and other hormones in human NAFLD.

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