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Non-alcoholic Fatty Liver Disease and Metabolic Syndrome in Hypopituitary Patients

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Abstract

Background—Increased incidence of cardiovascular mortality and non-alcoholic fatty liver disease (NAFLD) has been reported in hypopituitarism; but previous studies did not correct for obesity in these patients. Therefore it remained unclear if endocrine deficiency in hypopituitarism is associated with metabolic consequences independent of obesity. This study was designed to determine the burden of cardiovascular disease and NAFLD in hypopituitarism.

Methods—We performed a retrospective case-control analysis of hypopituitary patients at Veterans Affair Medical center, Memphis; from January 1997- June 2007. After matching for age, gender, obesity and race, relevant data were abstracted from the subjects' records to determine the presence of hypopituitarism, cardiovascular risk factors and fatty liver disease. Cases and controls were characterized by descriptive statistics, and compared using Chi-square and Student's t- tests.

Results—Hypopituitary patients exhibited higher prevalence of hypertension- 88% vs 78% ($P<0.03$), hypertriglyceridemia-80% vs 70% ($P=0.05$), low HDL cholesterol-84% vs 70% ($P<0.001$), and metabolic syndrome-90% vs 71% ($P<0.001$). Patients also had higher mean plasma glucose levels-228 ± 152 vs 181 ± 83 mg/dL ($P<0.01$). Despite higher preponderance of cardiovascular risk factors in hypopituitary patients, prevalence of cardiovascular morbidity was similar in both groups ($P>0.3$). Hypopituitary patients had higher elevations in serum aminotransferase levels and hyperbilirubinemia-24% vs 11% ($P<0.01$), as well as higher INR and hypoalbuminemia 40% vs 23% ($P<0.01$).

Conclusions—There is increased prevalence of metabolic syndrome and liver dysfunction consistent with NAFLD in hypopituitarism. Although hypopituitary patients had higher prevalence of cardiovascular risk factors than controls, they were not disproportionately affected by cardiovascular disease.

Keywords

cardiovascular risk; insulin resistance; metabolic syndrome

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It is now well established that patients with hypopituitarism, especially growth hormone deficiency have increased incidence of an insulin resistant syndrome, characterized by abdominal adiposity, dyslipidemia, hyperglycemia, hypertension and nonalcoholic fatty liver disease (NAFLD) (1-6). There have also been reports of increased cardiovascular morbidity and mortality in patients with hypopituitarism (7-12). Although available literature shows excess mortality in patients with pituitary deficiency, there are conflicting reports regarding the incidence of cardiovascular mortality in patients with hypopituitarism. While some studies have demonstrated increased cardiovascular events in patients with hypopituitarism (7,8,12), others have found no significant increase (9), or even a decrease in cardiovascular morbidity or mortality (10). A large prospective study (11), which was designed to resolve this conflict, confirmed increased mortality in patients with pituitary deficiencies, but greater mortality from respiratory and cerebrovascular diseases than from cardiovascular causes (Standard mortality ratios of 2.66, 2.44 and 1.82 respectively). It is also noteworthy that these studies used a normal population or age and sex matched cohort as comparator groups, but none of them were matched for the effect of obesity. This is even more significant, as compared with a normal population, obesity is more prevalent in patients with hypopituitarism. Therefore, it still remains to be shown if the excess mortality in patients with pituitary deficiency is due to cardiovascular events, triggered in part by increased incidence of metabolic syndrome and obesity.

There have been several anecdotal and observational reports of NAFLD in hypopituitary patients, most notably those with growth hormone deficiency (5,6,13-15), but these studies did not include comparator groups. Some of the reported cases had severe end stage liver disease, requiring liver transplantation (6,14). Recurrence of NAFLD after successful liver transplantation has also been reported (14), suggesting that correction of the perturbed metabolic milieu may be vital for the effective treatment of these patients. Against this background, we undertook a retrospective analysis of patients with varying degrees of hypopituitarism seen at the Veterans Affairs Medical Center in Memphis; with the view of estimating the degree of NAFLD in these patients. In addition, we were interested in the concomitant burden of cardiovascular risk factors induced by pituitary deficiency-associated obesity and metabolic syndrome.

METHODS

Study design and patient selection

We conducted a retrospective case-control analysis of patients seen in the endocrine clinic of the VAMC, Memphis; between January 1997 and June 2007. A list of all patients with hypopituitarism was obtained from the Computerized Patient Record System (CPRS) using ICD codes for pituitary disease. The control subjects were obtained from patients matched for age, gender, race and body mass index (BMI) using a list obtained from the Dermatology clinic of the Hospital. Patients with liver disease (hepatitis B or C, autoimmune, drug or alcohol-induced liver disease, cholestatic, inherited or metabolic liver disease such as Wilson's disease or hemochromatosis) were excluded. All patients who had documented pituitary deficiency, without the above mentioned liver diseases were included in the study. Records of selected patients were reviewed and relevant data collected.

Biochemical measurements

Pituitary reserve assessed by adrenal, thyroid, growth hormone and/or IGF-1 and gonadotrophin levels was determined by values from the biochemical tests in use at the time of investigation. Patients were judged as deficient if they had levels below the reference range determined by the laboratory. Patients were also considered deficient for the relevant axis if

they were already on hormone replacement at the time of their first visit. Other biochemical parameters such as liver enzymes and INR were interpreted based on the reference range for the laboratory.

Definitions

In order to compare the cardiovascular risk between the patients and control, we determined the proportion of patients who had metabolic syndrome using a modification of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP 111) criteria (16). We defined the metabolic syndrome as the presence of three or more of the following risk factors:

1. Obesity defined as Increased waist circumference (>102cm for men, >88cm for women) or BMI ≥ 30.
2. Elevated triglycerides (≥150 mg/dL).
3. Low HDL cholesterol (<40mg/dL in men, <50 mg/dL in women).
4. Hypertension (Systolic blood pressure ≥130 and/or diastolic pressure ≥85 mmHg).
5. Impaired fasting glucose (≥110 mg/dL) or random blood glucose ≥ 140 mg/dl. Patients with diabetes were classified as having met the abnormal blood glucose criterion.

The maximum reading for each of these parameters available in the records was used in this definition. Patients and controls were treated for these risk factors except when contraindicated, therefore, both patients and controls were categorized regardless of treatment status.

Where available, the etiology of hypopituitarism was further identified by neuroimaging using MRI or histopathology of the pituitary obtained after surgical resection. The diagnosis of NAFLD was made by abnormal liver function tests or imaging by ultrasound, CT, or liver histology where available. Diagnosis of NAFLD was made after medication toxicity and intercurrent illnesses had been excluded as possible etiology of hepatic dysfunction from the available records.

Statistical analysis

Data were analyzed using SAS software. Subjects were divided into groups that were characterized by descriptive statistics such as mean ± SD. Groups were compared using Student's t test and Chi-square tests.

Ethical consideration

This study involved human subjects and was conducted in accordance with clinical research standards of the Institutional Review Board of the VA Medical Center. Confidentiality was maintained in accordance with HIPAA regulations in force at the facility.

RESULTS

Demographic Characteristics of the Patients and Controls

The demographic profile of the patients and controls is shown in table 1; both groups were well matched in terms of age, gender, race and obesity. The average age of the cohort was 66.2 ± 11.9.

Etiology of Hypopituitarism

The underlying etiology of pituitary deficiency is illustrated in table 2. Some of the patients had been managed in other medical centers before transferring their care to our facility, therefore, the exact pathology that resulted in hypopituitarism was not known in some cases.

The distribution of deficiency in anterior pituitary hormones is shown in table 3. Nearly all the patients exhibited gonadotropin deficiency, but somatotropin insufficiency was found in three-quarters of the patients. Two-thirds of the cohort had thyroptropin, while slightly less than two-thirds had adrenocorticotropin deficiency. Prolactin deficiency was uncommon. Only 10% of the patients were deficient in one pituitary axis, the overwhelming majority of them demonstrated deficiency in two or more pituitary axes (see table 4).

Treatment for hypopituitarism

Patients with adrenal, thyroid and/or gonadotrophin deficiency received physiological replacement of the relevant hormones (cortisol, thyroxine, and/or testosterone). Sixty-three percent of the patients were treated with corticosteroids, while 66% and 80% of them received levothyroxine, and testosterone respectively. Some patients with gonadotrophin deficiency were not treated or had their treatment discontinued due to prostatic cancer, secondary polycythemia or patient's preference. No patient received growth hormone therapy. Subjects on hormone replacement were evaluated clinically and biochemically at regular intervals, according to standard clinical practice to ensure physiological replacement of the deficient hormones.

Cardiovascular risk factors in Hypopituitary Patients and controls

Table 5 shows the number of hypopituitary patients and controls who fulfilled the criteria for each of the risk factors used to define metabolic syndrome. In comparison with controls, patients showed a significantly higher prevalence of hypertension, hypertriglyceridemia, low HDL cholesterol and higher mean blood glucose levels. Overall, patients also had a higher preponderance of the metabolic syndrome than controls. However, as seen in table 6, both patients and controls had similar prevalence of cardiovascular morbidity. Table 7 demonstrates the effect of obesity on the prevalence of cardiovascular risk factors. In hypopituitary patients, the prevalence of metabolic syndrome and cardiovascular risk factors were similar in the obese and non-obese; whereas amongst controls, subjects with obesity were significantly more affected by the components of metabolic syndrome than the non-obese ($P < 0.0001$).

Abnormal liver function—The prevalence of abnormal liver function tests (LFTs) in hypopituitary patients and controls is illustrated in table 8.

Elevation in serum aminotransferases and bilirubin

Serum aminotransferase level was considered to be elevated if it was above the normal reference range for the laboratory. There was no significant difference between patients and controls in the number of subjects who had elevated aspartate aminotransferase (AST) levels {37% (52/139) vs 34% (44/131), P= 0.62}. However, patients had more severe elevations (4.3-fold compared to 2.9-fold in the control group). Similarly, the number of subjects who had elevated alanine aminotranferase (ALT) did not differ between patients and controls {36% (50/140) vs 35% (46/130)}, but hypopituitary patients had a higher degree of ALT elevations than controls (3.8-fold vs 2.3-fold).

There did not appear to be any difference between patients and controls in the level of alkaline phosphatase. Thirty-two percent of patients (45/139) had elevated alkaline phosphatase levels with mean value 1.8 times upper limit of normal, compared to 26% of controls (34/131) with mean level 1.4-times the upper limit of normal (P=0.29). Also, the mean level of γ-glutamyl transferase (GGT) was comparable between patients and control (3.9 vs 3.6 times normal).

Elevation in serum bilirubin

Hyperbiliruninemia was more prevalent in the patients with hypopituitarism 24% (33/138), compared to 11% (15/132) in the controls ($p<0.01$), Patients also exhibited a higher degree of hyperbilirubinemia than controls (4.1 vs 2.6 times normal).

Impaired hepatic protein synthesis

Forty percent of the patients with pituitary deficiency (58/141) had impaired production of coagulation proteins as evidenced by elevated INR as well as low serum albumin level, compared to 23 % of controls who were deficient in both measurements ($P< 0.01$). Hypoalbuminemia was significantly more prevalent in the hypopituitary group. Forty-three percent of the patients (58/135) had low serum albumin level, compared to 31% (40/130) of the control ($P<0.04$); see table 8.

Nonalcoholic fatty liver disease

In the patients with abnormal liver enzymes, seven of seventeen who had liver imaging performed had radiographic findings consistent with steatosis. In the five who had liver biopsy, steatosis or extensive fibrosis was documented in the absence of other etiologies for liver disease.

DISCUSSION

Using modified NCEP ATP 111 definition of metabolic syndrome, we have demonstrated that hypopituitarism is associated with significantly greater preponderance of cardiovascular risk factors, liver dysfunction consistent with NAFLD and metabolic syndrome. However, despite the higher prevalence of cardiovascular risk factors and metabolic syndrome in these patients, the prevalence of cardiovascular morbidity did not differ from that of matched controls. A modification of NCEP ATP 111 was adopted in this study because most subjects did not have waist circumference measurement. Therefore, in place of waist circumference, we assessed obesity by body mass index (BMI), with BMI ≥30 qualifying as obese. Secondly, it was difficult to ascertain which of the patients had true fasting plasma samples, therefore, in place of fasting plasma glucose; we used casual plasma glucose to evaluate for hyperglycemia. Plasma glucose levels ≥140 mg/dL were considered as abnormal; this included some patients with diabetes. These modifications may have overestimated hypertriglyceridemia and hyperglycemia. Furthermore, obesity is more precisely measured by waist circumference than BMI. We believe these modifications would not affect the results and conclusions of this study since patients and controls were treated in the same manner. We wish to point out that our patients had their pituitary deficiencies treated with the required target organ hormones, except for growth hormone which was not replaced. Although we believe our patients were adequately treated, it should be noted that excessive treatment with corticosteroids may result in features similar to metabolic syndrome.

The finding of hypertension, hyperglycemia, hypertriglyceridemia and low HDL in hypopituitary patients is consistent with previous studies (1,4,17). The observation in this study that the prevalence of cardiovascular risk factors was similar in the obese and non-obese hypopituitary patients, in contrast to the controls where obesity was associated with higher prevalence of risk factors, suggests that hypopituitarism per se is associated with metabolic syndrome independent of level of adiposity measured by BMI. This observed metabolic phenotype is thought to be a consequence of underlying insulin resistance which has been demonstrated in patients with hypopituitarism, particularly in the setting of growth hormone deficiency (1-2). Paradoxically, other studies in patients with liver cirrhosis observed that elevated rather than low growth hormone levels contributed at least in part to the etiology of insulin resistance, impaired glucose tolerance and diabetes in these patients (18,19). It is likely

that duration of growth hormone deficiency is of great importance here, as acute deficiency may be quite different from chronic deficiency.

Again, the higher prevalence of hepatic dysfunction consistent with NAFLD observed in this study is concordant with anecdotal reports and findings of other observational studies (5,6, 13-15). However, it is noteworthy that these studies did not have comparator groups, therefore, it remained unclear if the incidence of NAFLD in hypopituitary patients was due to obesity or the endocrine deficient state per se. The result of this study suggests that the high prevalence of abnormal liver function in hypopituitarism may be driven at least in part by the endocrine deficiency rather than obesity alone. Obesity combined with hypopituitarism may provide a larger residuum of nonesterified fatty acid (NEFA) for excess triglyceride production in the liver in an insulin-resistant state, thus leading to NAFLD. In humans with obesity, hypertriglyceridemia and hyperinsulinemia, the major mechanism for accumulation of excess hepatic triglyceride, accounting for about 60% of very low density lipoprotein (VLDL) production, is increased delivery of NEFA from expanded peripheral adipose tissue mass (20).

The pathophysiologic mechanism of insulin resistance in patients with hypopituitarism is not known with certainty, but available evidence suggests that interaction between growth hormone and leptin may play a role. Growth hormone is regulated by nutrients and metabolites such as free fatty acids (FFA), triglycerides, glucose and amino acids (21). It is well known that obesity is associated with blunted growth hormone response, whereas malnutrition and starvation are associated with elevated growth hormone levels, indicating a strong connection between nutrition status and growth hormone secretion (21). Leptin, an adipokine, constitutes the afferent arm of the connection between fat cell mass and the satiety center in the hypothalamus. Leptin acts on its receptor in the arcuate nucleus of the hypothalamus to induce anorexia and increased thermogenesis, thus producing a catabolic state that would lead to weight loss. Subjects with obesity have elevated leptin levels and demonstrate attenuated response to exogenously administered leptin, findings consistent with leptin resistance (22); but patients with hypopituitarism have been shown to have even higher levels of circulating leptin, independent of obesity, which suggests a higher degree of leptin resistance (23-25). This Leptin resistant state is analogous to insulin resistance in type 2 diabetes in which hyperglycemia occurs despite hyperinsulinemia (26). The finding in this study that hypopituitary patients are affected to the same degree by cardiovascular risk factors regardless of the level of obesity may be explained by the fact that hypopituitarism induces a higher level of leptin resistance than common obesity.

Inability of the hypothalamo-pituitary axis to respond to leptin, an anorectic hormone results in hyperphagia through unrestrained activity of orexigenic hormones like neuropeptide Y and Agouti-related peptide, thus resulting in obesity and insulin resistance (27,28). Although the etiology of leptin resistance in pituitary disease remains unclear, it is probable that low levels of growth hormone and IGF-1, which occur in most patients with hypopituitarism (75% in this study), result in loss of feedback within the hypothalamo-pituitary-adipose axis, thus creating a hyperleptinemic state. Growth hormone causes lipolysis resulting in increased FFA and possibly leptin levels. While FFA inhibits somatotropin release in the adenohypophysis, leptin interacts with GHRH and somatostatin-producing neurons in the arcuate nucleus of the hypothalamus to produce diminished growth hormone secretion (28).

There is also accumulating evidence implicating leptin in the pathogenesis of NAFLD. In patients with chronic hepatitis C infection, blood levels of leptin have been shown to correlate with the degree of hepatic damage (29). Secondly, Leptin-deficient obese diabetic mice were protected from hepatocellular damage when exposed to a hepatotoxic diet deficient in methionine and choline, suggesting that leptin may play a critical role in the induction of

NAFLD in rodents (30). Hyperleptinemia, which occurs in hypopituitarism may contribute to NAFLD by enhancing adipocyte production of proinflammatory cytokines like TNF α that may be hepatotoxic (31), and by inducing insulin resistance in hepatocytes through de-phosphorylation of insulin-receptor substrate 1 (32).

The finding of excess cardiovascular mortality or morbidity reported in other studies (7,8,12) was not replicated in this study; but our observation is in accordance with that of Bates et al (10), who did not record a significant increase in vascular disease in patients with hypopituitarism. The difference between these earlier reports and this study may lie in the fact that we corrected for the confounding influence of obesity. Although, the frequency of cardiovascular risk factors and metabolic syndrome was higher amongst patients with hypopituitarism in this study, the prevalence of cardiovascular disease measured by the composite end point of coronary artery disease, stroke and peripheral artery disease was similar in the two populations. This may be explained by the fact that these risk factors were equally and optimally treated in both patients and controls. In high risk diabetic patients, it has been shown that intensive intervention results in reduction in vascular complications and cardiovascular mortality (33). Secondly, the influence of other established cardiovascular risk factors such as smoking and family history of cardiovascular disease were not explored in this study. Lastly, it is possible that some other element of pituitary deficiency such as elevated INR in those with liver dysfunction may have protected against thrombotic cardiovascular phenomena, thus reducing the expression of cardiovascular disease.

This study has the combined strength of a fairly large population of hypopituitary patients and well matched controls, but also suffers the limitation of being subject to ascertainment bias due to its retrospective nature. Ancillary investigations such as liver function tests and liver imaging may have been done in those patients who were perceived to have some abnormality, thus excluding those patients who were clinically asymptomatic. This would have underestimated the prevalence of NAFLD in this study. Therefore while this study provides valuable data in this cohort with relatively uncommon disorder, a properly controlled prospective study would still be required to prove the suspected associations elicited in this study. None the less, our retrospective study clearly demonstrates that patients with hypopituitarism had higher prevalence of hypertension, diabetes mellitus, hyperlipidemia, metabolic syndrome and NAFLD, but no excess cardiovascular morbidity.

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Table 1

Demographic Characteristics of the Patients and Matched Controls.

	Patients	**Control**	**P**
Age	66.2 ± 11.9	66.0 ± 11.6	NS
Sex (F/M)	2/139	2/139	NS
Race			
Caucasian	77	77	NS
African-American	58	58	NS
Others	6	6	NS
BMI	34.1 ± 7.4	33.7 ± 6.8	NS

Table 2

Etiology of Hypopituitarism in our Patient Cohort

Underlying cause	Number of patients (%)
prolactinoma	5 (3.6)
Acromegaly	4 (2.8)
Empty sella syndrome	4 (2.8)
Arachnoid cyst	2 (1.42)
Cushing's disease	2 (1.42)
Craniopharyngioma	1 (0.71)
Meningioma	1 (0.71)
Trauma	1 (0.71)
Sarcoidosis	1 (0.71)
Unspecified pituitary adenoma	58 (41.1)
Unspecified pituitary tumor[+]	62 (44.0)
Total	141 (100)

[+]Patients were initially treated in other hospitals, but continued their care in our clinic; detailed records not available.

Table 3

Distribution of Anterior Pituitary deficiencies in our Patient Cohort

Axis	**Number of patients deficient (%), out of 141 patients.**[+]
Gonadotrophins	135 (95.7)
Growth hormone	105 (74.5)
Thyroid	94 (66.7)
Adrenal	90 (63.8)
Prolactin	24 (17.0)

[+]Patients were diagnosed as deficient for the relevant axis if the hormonal values were below the reference range in use in our laboratory at the time of evaluation (different reference ranges were used during the period of this study-1997-2007).

Table 4

Number of Pituitary Axes deficient in these (141) Patients

Axes	Number of patients (%)
1	14 (9.9)
2	47 (33.3)
3	41 (29.1)
4	39 (27.7)
Total	141 (100)

Table 5

Prevalence of cardiovascular risk factors in hypopituitary patients and Controls

Risk factors	Patients n=141	Control n=141	χ^2	P-value
Blood pressure ≥130/85mmHg	124	110	4.92	<0.02
Blood glucose[+] ≥140 mg/dL	96	86	1.55	>0.2
BMI ≥ 30	100	97	0.15	>0.6
Triglyceride ≥ 150 mg/dL	113	99	3.72	0.05
HDL ≤ 40 mg/dL	118	99	7.22	<0.01
Metabolic syndrome	126	100	15.06	<0.001

[+] Although, there was no difference between patients and controls in the proportion of people with blood glucose levels ≥ 140 mg/dL, patients had higher mean blood glucose levels than controls (227.8 ± 152 mg/dL vs 180.7 ± 83.3; t = 3.14, P < 0.01)

Table 6

Prevalence of cardiovascular disease (CVD) [coronary artery disease, cerebrovascular disease and peripheral artery disease] in Hypopituitary Patients and Matched Controls

CVD	Patients	Control	Total
Present	41	49	90
Absent	100	92	192
Total	141	141	282

$\chi^2 = 1.04$; $P > 0.3$

Table 7

Effect of obesity on the prevalence of cardiovascular risk factors in hypopituitary patients and controls

	Hypopituitary patients			Controls		
BMI Risk Factors	**BMI < 30, n=41**	**BMI ≥ 30, n=100**	**P-value**	**BMI < 30, n=42**	**BMI ≥ 30, n=99**	**P-value**
Blood Pressure ≥ 130/85 mmHg	35	89	>0.5	27	83	<0.01
Blood glucose ≥ 140 mg/dL	26	70	>0.4	19	83	<0.0001
Triglyceride ≥ 150g/dL	31	84	>0.2	27	80	<0.04
HDL ≤ 40 mg/dL	34	86	>0.6	24	80	<0.004
Metabolic syndrome	33	89	>0.1	16	83	<0.0001

Table 8

Prevalence and degree of abnormal LFTs in hypopituitary patients and controls

	Prevalence of abnormal LFTs			Fold increase above normal	
LFT indices	**Patients (%)**	**Controls (%)**	**P-value**	**Patients**	**Controls**
AST	37	34	>0.5	4.3	2.9
ALT	36	35	>0.5	3.8	2.3
Alk Phos	32	26	>0.1	1.8	1.4
Bilirubin	24	11	<0.01	4.1	2.6
Albumin	43	31	<0.04		
Albumin + INR	40	23	<0.01		