ORIGINAL ARTICLE

Cardiovascular disease, hypertension, dyslipidaemia and obesity in patients with hypothalamic-pituitary disease

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Objective: Adults with hypothalamic-pituitary disease have increased morbidity and mortality from cardiovascular disease (CVD). Therefore, the prevalence of CVD and adequacy of treatment of cardiovascular risk factors (according to current treatment guidelines) was studied in a large group of patients with hypothalamic-pituitary disease.

Study design: In 2005, 152 consecutive adult patients with hypothalamic-pituitary disease attending our neuro-endocrine centre were clinically examined and blood pressure (BP), lipid profile, type 2 diabetes mellitus, body composition and smoking status were assessed.

Results: Of the 152 patients, 36.8% had treated hypertension and 28.2% had treated dyslipidaemia. Many of these patients had inadequate BP control (BP >140/85 mm Hg, 44.6%) and undesirable lipid levels (total cholesterol >4.0 mmol/l, 69%). Also, many of the untreated patients had BP and lipid levels which should have been considered for treatment (26 patients (27%) and 83 patients (76%), respectively). Smoking was admitted in 18% of patients. Central adiposity was present in 86% and obesity (body mass index ≥ 30) was present in 50%.

Conclusions: Cardiovascular risk factors are highly prevalent and often inadequately treated in adult patients with hypothalamic-pituitary disease. Aggressive treatment of these factors is essential to reduce mortality and morbidity from CVD in these patients.

Several studies over the last 15 years suggest that cardiovascular morbidity and mortality are increased in adult patients with hypothalamic-pituitary disease.^{1–4}

Many of these patients have chronic growth hormone deficiency (GHD), which is associated with significant cardiovascular risk factors including centrally distributed adiposity, dyslipidaemia, reduced insulin sensitivity, hypertension and abnormal haemostatic factors.⁵ Patients with functioning pituitary tumours causing acromegaly and Cushing's disease have an increased prevalence of impaired glucose tolerance, type 2 diabetes mellitus and hypertension, also causing an increased cardiovascular risk.^{6,7}

The aims of this study were to determine the prevalence of macrovascular disease and adequacy of treatment of hypertension, dyslipidaemia and type 2 diabetes mellitus in a cohort of patients with hypothalamic-pituitary disease. We also studied the prevalence of obesity and body composition in these patients. This information is obviously valuable in planning treatment strategies for the cardiovascular risk factors in these patients.

METHODS

In 2005, the data were recorded in 152 consecutive patients with hypothalamic-pituitary disease who attended the neuro-endocrine clinic as described below.

Sitting blood pressure (BP) was measured according to the guidelines of the Joint British Societies (JBS)⁸ (hypertension was defined as sustained systolic BP (SBP) >140 mm Hg and/or diastolic BP (DBP) >90 mm Hg). The aim of BP treatment is to achieve a BP target of <140 mm Hg systolic and <85 mm Hg diastolic (<130/80 mm Hg in those with diabetes mellitus) in these patients in view of their cardiovascular risk.

In the non-fasting state, the following were measured: random venous plasma glucose, glycated haemoglobin (HbA_{1c}) and serum lipid profile (total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglycerides). In this study, we

assessed if patients had achieved a target TC of <4.0 mmol/l and LDL-C of <2.0 mmol/l as recommended in the JBS 2 guidelines.⁸

In most patients, body mass index (BMI, kg/m²), waist circumference (WC), hip circumference and waist hip ratio, and body fat percentage (assessed by whole body bio-electrical impedance analysis; Tanita Systems, Stokie, IL) were also measured.

We also recorded the prevalence of established cardiovascular disease (CVD) in these patients, that is, ischaemic heart disease (IHD), cerebrovascular disease (cerebrovascular accident (CVA) or transient ischaemic attack (TIA)) and peripheral vascular disease (history of intermittent vascular claudication). Additionally, family history of premature CVD (coronary heart disease or stroke in male first degree relatives aged <55 years and female first degree relatives aged <65 years) and current smoking status were also recorded.

Regular endocrine assessments were made to identify and correct pituitary hormone deficiencies, including GHD. All patients had at least annual measurement of random serum hormones (free T₄, free T₃, prolactin, LH, FSH, testosterone or oestradiol, cortisol and insulin-like growth factor 1 (IGF-1)). Depending on the primary hypothalamic-pituitary diagnosis, previous surgery and/or radiotherapy, dynamic pituitary testing of ACTH and GH secretion was carried out using the glucagon test.⁹

Patients received full appropriate pituitary hormone replacements. Over the last decade GH replacement has been offered, when appropriate, to patients with severe, symptomatic GHD (stimulated growth hormone level ≤ 9.0 mIU/l and poor quality

Abbreviations: BMI, body mass index; BP, blood pressure; CVA, cerebrovascular accident; CVD, cardiovascular disease; DBP, diastolic BP; GHD, growth hormone deficiency; HDL-C, HDL-cholesterol; IHD, ischaemic heart disease; JBS, Joint British Societies; LDL-C, LDL-cholesterol; SBP, systolic BP; TC, total cholesterol; TIA, transient ischaemic attack; WC, waist circumference

Table 1 Diagnoses, treatments and prevalence of cardiovascular disease in the 152 patients studied in 2005

	n	Age (years)	Sex (M:F)	TSS*	Cranial surgery	External radiation†	Treated hyper-tension	Treated dyslipid-aemia	Diabetes mellitus	Athero-sclerotic CVD
Total	152	52±14	89:63	59.8	13.8	33.5	36.8	28.2	9.2	9.2
Diagnosis										
NFPA‡	66	61±12	40:26	88.5	0	22.7	42.4	31.8	7.5	12
Acromegaly	18	56±15	9:9	94.4	0	50	55.6	33.3	16.7	22
Cushing's disease	5	46±15	1:4	100	0	20	40	20	40	0
Macroprolactinoma	21	47±12	16:6	28.5	9.5	23.8	19	9.5	9.5	0
Craniopharyngioma and Rathke cysts	17	46±15	9:8	23.5	58.8	41.7	29.4	35.2	5.8	0
Other intracranial tumours§	12	41±10	5:7	8.3	66.6	100	25	25	0	8.3
Miscellaneous¶	13	40±10	9:4	0	8.3	16.6	23	15.3	7.7	0
Hormone replacement therapy	%									
Cortisol	62.5									
Thyroxine	44									
Sex steroids	47.3									
Growth hormone	38.1									
Desmopressin	11.8									

Data are mean ± SD and percentages.

*Trans-sphenoidal surgery; †external irradiation involving pituitary and/or hypothalamus; ‡non-functioning pituitary adenoma; §glioma (n=2), medulloblastoma (n=1), meningioma (n=1), unclassified brain tumour (n=1), chordoma (n=3), pinealoma (n=1), lymphoma (n=1), suprasellar germinoma (n=1), nasopharyngeal tumour (n=1); ¶idiopathic hypopituitarism (n=5), empty sella (n=3), trauma (n=1), acute lymphocytic leukaemia (n=1), Langerhans cell histiocytosis (n=1), birth asphyxia (n=1), transfusional iron overload (n=1).

of life as measured by the Assessment of Growth Hormone Deficiency in Adults (AGHDA) questionnaire).¹⁰

RESULTS

Table 1 shows details of the 152 patients. The most common disorder was non-functioning pituitary adenoma (NFPA, 43.4%) followed by prolactinoma (14.4%).

The table also lists the prevalence of treated hypertension (36.8%), dyslipidaemia (28.2%), diabetes mellitus (9.2%), atherosclerotic CVD (11.1%), smoking history (current smokers 18.4%) and family history of premature CVD (14.4%) in these patients. The atherosclerotic CVD events included 12 IHD (myocardial infarction and stable angina pectoris), four patients with cerebrovascular episodes (two CVA and two TIA) and one patient with peripheral vascular disease.

Blood pressure and lipid profiles

The actual BP and serum lipid measurements are shown in table 2. The mean (±SD) SBP and DBP in the group collectively were 136±22 and 82±11 mm Hg, respectively. Fifty six patients (36%) were already taking anti-hypertensive medications and in this treated sub-group mean (±SD) BP was 148±20/86±10 mm Hg. Despite treatment, 44.6% of these patients still had suboptimal measurements (>140 mm Hg systolic and/or >85 mm Hg diastolic). Of the 96 patients not on pharmacological treatment for hypertension, 27% had BP readings that would have warranted treatment. Of the 14 patients with type 2 diabetes mellitus, mean (±SD) BP among those with known hypertension was 143±11/82±8 mm Hg (target <130/80 mm Hg).

Results for the 42 patients (27%) who were taking lipid-lowering therapy demonstrated mean (±SD) TC 4.8±0.9 mmol/L, LDL-C 2.2±0.7 mmol/L and HDL 1.3±0.3 mmol/L. Despite lipid lowering therapy, 69% of treated patients had TC >4.0 mmol/L and 85% had LDL-C >2.0 mmol/L, reflecting suboptimal treatment. Of the patients not taking lipid-lowering therapy (n=110), mean TC was 5.6±0.9 mmol/L, LDL-C 3.1±0.8 mmol/L and HDL-C 1.3±0.4 mmol/L; many of these patients should be considered for pharmacological intervention.

Diabetes mellitus

Of the 14 patients with known type 2 diabetes mellitus, (mean) metabolic control was good (HbA_{1c} 6.75±1.09%). Mean

random plasma glucose among the "non-diabetic" patients was 5.24±0.8 mmol/L and no patients were newly diagnosed with diabetes.

Obesity and body composition

Obesity, defined as BMI ≥30,¹¹ was prevalent in 50% of patients, 30.8% were overweight (BMI ≥25–29.9) and only 19% were of normal body weight. Of the 60 patients who were obese, 32 (26.6%) had class I obesity (BMI 30–34.9), 14 (11.6%) had class II obesity (BMI 35–39.9) and 14 patients (11.6%) were morbidly obese (BMI ≥40). The mean WC was 103.4±13.9 cm indicating the majority (86%) had central obesity (WC ≥94 cm for Europid men and ≥90 cm for Europid women).¹²

Male patients were more abdominally obese and had higher waist hip ratio than women, although women tended to have a higher proportion of total body fat (41.9±6.9% v 29.3±6.8%, p=not significant) (table 3).

DISCUSSION

There exists a large body of evidence confirming the substantial benefits of BP reduction,^{13–15} lipid lowering treatment^{16–17} and modest weight loss¹⁸ in the general population for reducing morbidity and mortality from major cardiovascular events such as IHD, stroke and heart failure.

Patients with hypothalamic-pituitary disease are known to have increased cardiovascular risk. In this study, treated hypertension was prevalent in 36.8% of patients, dyslipidaemia in 28.2%, type 2 diabetes mellitus in 9.2% and CVD (mostly IHD) in 9.2%. BP was suboptimally treated in 44.6% of patients and lipid profiles were not to target in over two thirds of patients already on lipid lowering treatment. However, it should be noted that if the earlier JBS 1 guidelines, published in 1998, were applied, 52% of patients could be considered to have achieved lipid targets, that is, TC <5.0 mmol/L and LDL-C <3.0 mmol/L. Also, many patients who were not on treatment for high BP or dyslipidaemia, had levels which would have warranted treatment according to current clinical practice guidelines.⁸

CVD was more prevalent amongst patients with non-functioning pituitary adenoma, probably reflecting the greater age of the group. Hypertension and diabetes were common in patients with acromegaly and Cushing's disease, as expected.

Table 2 Blood pressure and serum lipid profiles according to pharmacologic treatment in patients studied in 2005

Risk factor	All patients (n = 152), mean $\pm$ SD	Patients taking anti-hypertensive drugs (n = 56, 36%)	Patients NOT taking anti-hypertensive drugs (n = 96, 64%)
Blood pressure, SBP/DBP (mm Hg)*	136 $\pm$ 22/82 $\pm$ 11	148 $\pm$ 20/86 $\pm$ 10 (44.6% (n = 25) of recordings >140 mm Hg SBP and/or >85 mm Hg DBP, ie uncontrolled BP*)	129 $\pm$ 19/79 $\pm$ 12 (27.1% (n = 26) of recordings >140 mm Hg SBP and/or >85 mm Hg DBP, ie requiring drug treatment*)
Lipid profile (non-fasting) (mmol/l)†		Lipid lowering treatment (n = 42, 27%)	No lipid lowering treatment (n = 110, 72%)
TC	5.4 $\pm$ 1.02	4.8 $\pm$ 0.9 (>4.0, 69%)	5.6 $\pm$ 0.9 (>4.0, 76%)
LDL-cholesterol	2.87 $\pm$ 0.9	2.2 $\pm$ 0.7 (>2.0, 85%)	3.1 $\pm$ 0.8 (>2.0, 44%)
HDL-C	1.3 $\pm$ 0.4	1.3 $\pm$ 0.3	1.3 $\pm$ 0.4
Triglycerides	2.56 $\pm$ 1.3	2.6 $\pm$ 1.4	2.5 $\pm$ 1.2

*Accepted target for BP control: <140/<85 mm Hg (in patients with diabetes: <130/<80 mm Hg); †accepted target for lipids: <4.0 mmol/l TC and <2.0 mmol/l LDL-C.

A major finding in the patients studied in detail was the prevalence of obesity (BMI $\geq$ 30), which was present in 50%. This was predominantly central adiposity, particularly in men. This is similar to the prevalence of obesity (52%) in patients with type 2 diabetes attending the diabetes clinic at the same hospital¹⁹ and nearly double the prevalence of obesity among both sexes in the UK general population. According to the Health Survey for England, in 2004, 29.6% of men and 25.8% of women were obese (BMI $\geq$ 30) (data for middle aged men and women).²⁰

The cause of obesity in these patients is multifactorial. Obesity is associated with lesions (congenital or acquired) of the hypothalamus due to damage to centres regulating appetite and feeding. In a recent study from this unit,²¹ 78.5% of adult patients with structural hypothalamic damage were obese. Our present study had a heterogeneous mix of patients with various hypothalamic-pituitary pathologies and only a minority had tumour involvement of the third ventricle or hypothalamus. Also, physical activity and mood can influence energy expenditure and body weight. Multiple aspects of quality of life, for example energy levels and psychological morbidity, are impaired in GHD patients and often these do not normalise in spite of growth hormone replacement.²²

In the light of evidence for excess mortality from CVD in patients with hypothalamic-pituitary disease,¹⁻⁴ this study is important as it reveals a large number of potentially modifiable cardiovascular risk factors within this population which should

be managed aggressively. This has resource implications and physicians managing these patients should actively screen and identify cardiovascular risk factors as well as manage the primary hypothalamic-pituitary problem. This includes consideration of pharmacological treatments for hypertension and dyslipidaemia and treating these to target. In particular, this study highlights a major need for weight reduction strategies. Weight loss is difficult to achieve in many patients and more difficult to sustain in most. It is important that appropriate lifestyle advice is given to these patients and that drug therapies (eg, orlistat, sibutramine, rimonabant) to aid weight reduction are considered. Patients embarking on a weight loss regimen will require access to dietetic services. Also smoking cessation programmes must be instituted.

For patients with diabetes mellitus, there are national²³⁻²⁵ and international guidelines²⁶ for management of hypertension and dyslipidaemia. However, despite the high cardiovascular burden in patients with hypothalamic-pituitary disease, no such specific guidelines exist for cardiovascular risk factor management in this group of patients, although "reversal of increased long-term mortality" is recommended as an objective of treatment in all patients with pituitary tumours.²⁷

In summary, we have demonstrated a high prevalence of modifiable cardiovascular risk factors, including hypertension, dyslipidaemia, obesity and smoking, in patients with hypothalamic-pituitary disorders, despite appropriate hormone replacement, including GH. A significant proportion also have established CVD and in this subgroup it is of even greater importance to identify and treat modifiable risk factors as a secondary prevention strategy. Obesity, with its association with type 2 diabetes and the metabolic syndrome, is a major problem for these patients. All these cardiovascular risk factors are easily identifiable and should be managed appropriately to reduce the burden of premature cardiovascular morbidity and mortality in this subgroup of patients.

Table 3 Anthropometric parameters for patients studied in 2005

Anthropometric measure	
BMI (kg/m ²)	31.2 $\pm$ 7.3
All patients	120
BMI $\leq$ 25.0	23
BMI 25.0–29.9	37
BMI $\geq$ 30	60
Obesity classes (BMI $\geq$ 30)	60
Class 1 (BMI 30–34.9)	32
Class 2 (BMI 35–39.9)	14
Morbid obesity (BMI $\geq$ 40)	14
Waist circumference (cm)	
Males, n = 52	107.1 $\pm$ 11.6
Females, n = 34	97.7 $\pm$ 15.5
Waist hip ratio	
Males, n = 52	0.97 $\pm$ 0.06
Females, n = 34	0.87 $\pm$ 0.07
Body fat (%)	
Males, n = 39	29.3 $\pm$ 6.8
Females, n = 27	41.9 $\pm$ 6.9

Data are expressed as numbers of patients or mean $\pm$ SD.

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