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ORIGINAL ARTICLE

Homocysteine levels in acromegaly patients

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Abstract

Acromegaly is associated with a two to three-fold increase in mortality related predominantly to cardiovascular disease. The excess mortality is associated most closely with higher levels of growth hormone (GH). Survival in acromegaly may be normalized to a control age-matched rate by controlling GH levels; in particular, GH levels less than 2.5 ng/mL are associated with survival rates equal to those of the general population. Hyperhomocysteinemia has also been recognized as a risk factor for cardiovascular disease, yet there are limited data on the prevalence of hyperhomocysteinemia in patients with acromegaly.

Eighteen acromegaly patients (7 male, 11 female, mean age 42.8 ± 11.0 years) in our endocrine clinic consented to having the following tests performed: complete blood count (CBC), thyroid hormones, folic acid, vitamin B12, plasma homocysteine levels, uric acid, fibrinogen, CRP, fasting glucose, insulin, C-peptide, total serum cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, GH, insulin-like growth factor-1 (IGF-1) and GH levels after an oral glucose tolerance test (OGTT). By history, fourteen had macroadenomas and four had microadenomas; eight had hypertension; two had glucose intolerance, and four had diabetes. Fifteen had had transsphenoidal or transfrontal surgery: two had been cured, but 13 others were taking long-acting octreotide. Five patients had undergone radiotherapy and the acromegaly in two was treated primarily with long-acting octreotide. CBC, thyroid hormone, folic acid, and vit B12 levels were normal in all patients. We divided the patients into two groups according to mean GH levels after an OGTT: Group 1 (GH<2.5 ng/mL, n=10), and Group 2 (GH≥2.5 ng/mL, n=8). Comparison of the two groups using Mann-Whitney U testing revealed statistically significant lower levels in Group 1 of the following parameters: GH (1.91 ± 0.90 vs. 8.58 ± 5.55 ng/mL, p=0.002), IGF-1 (338.30 ± 217.90 vs. 509.60 ± 293.58 ng/dL, p=0.06), GH after an OGTT (1.42 ± 0.81 vs. 9.01 ± 4.53 ng/mL, p=0.001), plasma homocysteine (12.85 ± 4.47 vs. 18.20 ± 4.99 µmol/L, p=0.05), total cholesterol (164.0 ± 20.81 vs. 188.0 ± 22.26 mg/dL, p=0.05) and LDL cholesterol (81.0 ± 9.64 vs. 116.70 ± 13.03 mg/dl, p=0.01). Differences between the other parameters were not significantly different. Acromegaly patients with high GH levels after an OGTT have much higher levels of homocysteine than patients with lower GH levels. The role of elevated homocysteine levels as an independent cardiovascular risk factor in the mortality of acromegaly patients should be determined in future studies.

Introduction

Acromegaly is an insidious disorder caused by a pituitary growth hormone (GH) – secreting adenoma resulting in high circulating levels of GH and IGF-1 [3]. It is associated with a two to three-fold increase in mortality related predominantly to cardiovascular disease. The excess mortality is closely related to levels of GH. Survival in acromegaly may be predicted by examining GH levels in particular age groups; in particular, GH levels less than 2.5 ng/mL have been described as being in a 'safe range', and are associated with survival rates equal to those of the general population [1,3,4,6].

Hyperhomocysteinemia has also been recognized as a risk factor for cardiovascular disease [7], yet there are limited data [2,5] on the prevalence of hyperhomocysteinemia in patients with acromegaly.

The aim of our study was to determine plasma levels of homocysteine in acromegaly patients with levels of GH above and below the generally accepted 'safe level' (2.5 ng/mL), and measure other cardiovascular risk markers.

Materials and methods

Patients

Eighteen acromegaly patients (7 male, 11 female, mean age 42.8 ± 11.0 years) in our endocrine clinic consented to having the following tests performed: complete blood count (CBC), thyroid hormones, folic acid, vitamin B12, plasma homocysteine, uric acid, fibrinogen, C-reactive protein(CRP), fasting glucose, insulin, C-peptide, total serum cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, GH, insulin-like growth factor-1 (IGF-1) and GH levels after an oral glucose tolerance test (OGTT). By history, fourteen had macroadenomas and four had microadenomas; eight had hypertension; two had glucose intolerance, and four had diabetes. Fifteen had had transsphenoidal or transfrontal surgery: two had been cured, but 13 others were taking long-acting octreotide. Five patients had undergone radiotherapy, and the acromegaly in two was treated primarily with long-acting octreotide. CBC, thyroid hormone, folic acid, and vitamin B12 levels were normal in all patients.

We divided the patients into two groups according to mean GH levels after an OGTT: Group 1 (GH<2.5 ng/mL, n=10), and Group 2 (GH≥2.5 ng/mL, n=8).

Assays

Serum GH levels were measured by chemiluminescent immunumetric assay using the DCP Immulite® hGH kit. Serum IGF-1 levels were determined by radioimmunoassay (Biosource Europe S. A., Nivelles, Belgium). Insulin and C-peptide levels were measured by RAI (IDS, USA). Serum fasting glucose, total cholesterol, HDL cholesterol, triglyseride, uric acid levels were measured by enzymatic methods using an Olympus 5200 Auto Analyzer® (Ireland). LDL cholesterol was calculated. Vitamin B12 and folate were measured by chemiluminescent assay using commercially available assay kits in a hormone analyzer (Advia Centaur System®, Bayer, USA). CRP was measured using a commercially available assay kit in a nephelometer (Beckman Array 360 System™, Ireland). Quantitative determinations of fibrinogen level in plasma were made using a commercially available assay kit in a coagulometer (Instrumentation Laboratory, ACL Futura plus®, USA). Plasma homocysteine level were determined by high performance liquid chromatography with fluorometric detection.

Statistical analysis

Statistical analyses (descriptive, Mann-Whitney U, and Spearman correlation tests) were performed using SPSS for Windows® (version 10.0; SPSS Inc., Chicago, USA). Statistical comparisons between groups were made using Mann-Whitney U test. Spearman correlation test was used to investigate the correlation between parameters. Data are expressed as mean ± SD.

Results

Demographic information and biochemical parameter results from our acromegaly patients are shown in Tables 1 and 2, respectively. Comparison (using Mann-Whitney U testing) of Group 1 (GH<2.5 ng/mL) and Group 2 (GH≥2.5 ng/mL) patients revealed statistically significant lower levels in Group 1 of the following parameters: GH (1.91 ± 0.90 vs. 8.58 ± 5.55 ng/mL, p=0.002), IGF-1 (338.30 ± 217.90 vs. 509.60 ± 293.58 ng/dL, p=0.06), GH after an OGTT (1.42 ± 0.81 vs. 9.01 ± 4.53 ng/mL, p=0.001), plasma homocysteine (12.85 ± 4.47 vs. 18.20 ± 4.99 μM, p=0.05), total cholesterol (164.0 ± 20.81 vs. 188.0 ± 22.26 mg/dL, p=0.05) and LDL cholesterol (81.0 ± 9.64 vs. 116.70 ± 13.03 mg/dl, p=0.01). Differences between the other parameters were not significantly different (Table 2). There was no correlation among parameters.

Discussion

Attempts to explain the role of homocysteine in the increase in cardiovascular mortality among acromegaly patients have only recently been undertaken. We found homocysteine, total cholesterol, and LDL cholesterol levels to be lower in acromegaly patients in the 'safe range' of GH levels. This is similar to the results of Jallad et al [2], in their population of untreated acromegaly patients, who found higher homocysteine levels in patients with high GH levels after OGTT. Our results conflict however with those of Sesmilo et al [5] in their study of 48 acromegaly patients, whose homocysteine levels were not significantly different than that of 47 controls (8.4 μM vs. 8.8 μM).

Human and animal studies support the concept that elevated homocysteine may be an independent risk factor for atherosclerosis, and patients with severe hyperhomocysteinemia experience higher rates of

Table 1. Demographic characteristics of acromegaly patients

	Group 1 GH<2.5ng/mL (n=10)	Group 2 GH>2.5ng/mL (n=8)
Gender (female/male)	6/4	5/3
Age (years)	43.30 ± 10.88	42.14 ± 12.07
Macroadenomas/microadenomas	8/2	6/2
Transsphenoidal or transfrontal surgery	8	7
Radiotherapy	4	1
Long-acting octreotide treatment	9	6
Hypertension (yes/no)	4/6	3/5
Impaired glucose tolerance / Diabetes mellitus	1/2	1/2

Table 2. Biochemical parameters in acromegaly patients

	Group 1 GH<2.5ng/mL (n=10)	Group 2 GH>2.5ng/mL (n=8)	p value
GH (normal range (nr):1–5 ng/mL)	1.91 ± 0.90	8.58 ± 5.55	0.002
GH after OGTT (ng/mL)	1.42 ± 0.81	9.01 ± 4.53	0.001
IGF-1 (nr: 69–358 ng/dL)	338.30 ± 217.90	509.60 ± 293.58	0.06
Homocysteine (nr: 0–12.0 μM)	12.85 ± 4.47	18.20 ± 8.99	0.05
Total cholesterol (nr: 112–200 mg/dL)	164.00 ± 20.81	188.00 ± 22.26	0.05
HDL cholesterol (nr: 35–75 mg/dL)	44.00 ± 9.3	44.50 ± 9.90	NS
LDL cholesterol (nr: 0–130 mg/dL)	81.00 ± 9.64	116.70 ± 13.03	0.01
Triglyceride (nr: 50–200 mg/dL)	135.10 ± 48.68	141.00 ± 86.06	NS
Fasting glucose (nr: 70–105 mg/dL)	80.66 ± 28.91	97.60 ± 16.50	NS
Insulin (nr: 6.0–27 μIU/mL)	6.95 ± 3.48	10.93 ± 5.25	NS
C-peptide (nr: 0.9–4.0 ng/mL)	2.80 ± 1.14	3.2 ± 1.10	NS
Fibrinogen (nr: 212–488 mg/dL)	448.50 ± 78.08	454. 90 ± 86.44	NS
CRP (nr: 0.0–0.8 mg/dL)	0.48 ± 0.47	0.46 ± 0.40	NS
Uric acid (nr: 2.6–7.2 mg/dL)	4.65 ± 1.45	5.56 ± 1.28	NS
Vitamin B12 (nr: 211–911 pg/mL)	416.20 ± 99.08	430.12 ± 84.25	NS
Folic acid (nr: 1.1-20 ng/mL)	11.3 ± 3.1	12.5 ± 4.2	NS

nr: normal range
NS: not significant

thrombolic events at a young age. In the literature yet there are limited data on the prevalence of hyperhomocysteinemia in patients with acromegaly.

Epidemiological studies have shown that the increased mortality associated with GH excess is reversed to normal rates in patients achieving 'safe' GH levels (<2.5 ng/mL), regardless of the therapeutic approach used. Elevated serum homocysteine levels have also been found to be associated with increased cardiovascular risk. In future studies of cardiovascular morbidity and mortality among acromegaly patients, the role of homocysteine levels, as well as GH levels, should be determined.

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