CLINICAL STUDY

Observational study in adult hypopituitary patients with untreated growth hormone deficiency (ODA study).

Socio-economic impact and health status

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Abstract

Objective: The aim of the present study was to assess the socio-economic impact at baseline and after one year of follow-up of clinical and health status characteristics and laboratory tests of adult-onset GH deficiency (AGHD), a well-known clinical entity, in a large group of Spanish hypopituitary patients with untreated AGHD.

Design and Methods: A total of 926 eligible patients with GHD (GH ≤ 5 ng/ml after stimulation) and at least one further pituitary hormone deficiency were retrospectively studied; 356 of these were followed for one year. Complete physical examination, IGF-I, lipid and routine biochemistry measurements and health-related quality of life (HRQoL) with the specific QoL-Assessment of Growth Hormone Deficiency in Adults (AGHDA) questionnaire were assessed at baseline and at 12 months in the prospective study. Health status and health–economic evaluation were measured by a specific questionnaire and a patient diary and compared with Spanish population study results.

Results: Clinical characteristics and laboratory tests of AGHD showed a higher incidence of cardiovascular risk factors and mortality compared with the general population (hypercholesterolaemia in 29% vs 18% and hypertension in 22.1% vs 14.9%). QoL-AGHDA scores for patients were significantly worse (P<0.01) and direct health costs were higher than in the general population.

Conclusions: Hypopituitary GHD adults had more cardiovascular risk factors, higher mortality, worse HRQoL and higher absolute health costs than the general population in Spain.

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Introduction

Growth hormone (GH) deficiency (GHD) in children leads to impaired growth and consequently short final height. Substitution therapy with GH in children has proved to favour linear growth and is normally used in this kind of patient. Although GH is secreted throughout life, its role in adulthood has only been studied in the last few years. GHD in adults is now a recognized clinical entity characterized by an increase in total fat mass, a reduction in lean body mass, reduced exercise capacity, decreased bone mass and impaired psychological well-being (1–6). On the other hand, therapy with GH in GH-deficient adult patients has been shown to normalize body composition, increase bone density and cardiac function, improve physical and health-related quality of life (HRQoL), raise insulin-like growth factor (IGF)-I serum levels and may exert beneficial effects on lipid metabolism (7–14).

At present, trials in GHD adults are mainly focused on assessing short- and long-term health consequences of the deficiency and its substitution treatment with GH. The more extensive and detailed our knowledge of the clinical, psychological and social features of this population, the more rational our use of GH in these patients can be. To date, information on these features, particularly socio-economic aspects and HRQoL in a large group of patients who acquire GHD in adulthood has not been sufficient. Therefore, a retrospective evaluation and one-year follow-up in a large group of Spanish patients with GHD acquired in adulthood, who were not treated with GH, was undertaken.

Objectives

The first objective was to undertake a study of Spanish GHD patients who acquired GH deficiency in adulthood...
obtained from the hospital records. Therapy and cause of death, if it occurred, were also stimulation tests and age at diagnosis. Pituitary disease for demographic data, aetiology of GH deficiency, GH at diagnosis. Acromegalic and previously GH-treated (GH values from hypothalamic–pituitary disease and GH deficiency included. Inclusion criteria required patients to suffer from non-GH pituitary deficiencies and to be aged ≥ 18 years at diagnosis. Acromegalic and previously GH-treated patients were excluded. Hospital records were reviewed for demographic data, aetiology of GH deficiency, GH stimulation tests and age at diagnosis. Pituitary disease therapy and cause of death, if it occurred, were also obtained from the hospital records.

Subjects and methods

Cross-sectional study

For the first objective, 926 eligible patients (485 females, 441 males; mean age: 53.3 years; S.D.: 14.7) from hospital records of endocrinology units of 37 reference hospitals distributed in the 17 Spanish autonomous regions were included. Inclusion criteria required patients to suffer from hypothalamic–pituitary disease and GH deficiency (GH values ≤ 5 ng/ml after a standard stimulation test), to have at least one other pituitary hormone deficiency, to be on stable and adequate replacements of the other non-GH pituitary deficiencies and to be aged ≥ 18 years at diagnosis. Acromegalic and previously GH-treated patients were excluded. Hospital records were reviewed for demographic data, aetiology of GH deficiency, GH stimulation tests and age at diagnosis. Pituitary disease therapy and cause of death, if it occurred, were also obtained from the hospital records.

Longitudinal study

A total of 356 patients (201 females, 155 males; mean age: 52.4 years; S.D.: 13.6) of the initial 926 were included in the follow-up study. Additional criteria required to enter this study were standard and stable replacement treatment for other pituitary hormone deficiencies for at least six months prior to inclusion, and GH deficiency diagnosed at least 12 months before. Recruitment period for this follow-up study was six months to avoid any time bias in the health year cost evaluation. Exclusion criteria were previous GH treatment and gonadotrophin deficiency with no oestrogen substitution for other pituitary hormone deficiencies. Serum IGF-I samples at baseline were analysed by a competitive radioimmunoassay (RIA). Serum IGF binding protein (IGFBP)-3 at baseline was measured by an enzyme-linked immunosorbent assay (ELISA) developed by Diagnostic System Laboratories Inc. (Webster, TX, USA). Both measurements were centralized in Pharmacia & Upjohn Laboratories – Peptide Hormones, Stockholm, Sweden. Patients were studied at baseline and at 12 months for blood analysis, electrolytes, general biochemistry with a lipid profile (total cholesterol, triglycerides, low and high density lipoprotein (LDL and HDL) cholesterol), liver and kidney function measured by standard techniques.

Health-related quality-of-life (HRQoL) assessment

The Assessment of Growth Hormone Deficiency in Adults questionnaire (QoL-AGHD-A) is a self-administered instrument specifically designed to evaluate HRQoL in GHD adults (16–18). The instrument was designed for use in clinical trials and the routine monitoring of GHD patients. It was developed in the United Kingdom from transcripts of in-depth interviews with adult GHD patients, which were analysed to determine which aspects of the condition were most commonly cited as incapacitating patients in the achievement of their needs. It has been translated and validated in several languages (Swedish, German, Italian and Spanish), thereby providing an instrument suitable for use in international studies (16–18). The QoL-AGHD-A contains 25 items with a yes/no response format. The total score is obtained by totalling the number of affirmative answers indicating presence of HRQoL problems with possible scores ranging from 0 (best HRQoL) to 25 (worst HRQoL). Data are expressed as mean scores and 95% confidence intervals (CI) adjusted for age and education level. Patients were compared with a random Spanish population sample of 963 subjects matched for age and sex to figures of the Spanish census.

Health status evaluation

The survey conducted by CIRES (Centro de Investigaciones Sobre la Realidad Social) included assessment of the following areas: state of health during the last year, health habits, social aspects (income, job, educational level, psychological or mood status) and economic data. In each hospital, the questionnaire was answered by the patients and conducted by the same interviewer. These results were compared with those obtained with the same survey carried out in a control population sample of 1200 normal Spanish subjects in February 1994 (19).

Methods

Physical examination

Physical examination included weight, height, body mass index (BMI), waist-hip ratio and blood pressure. Results were compared with reference standards of an adult Spanish population.

Laboratory evaluation

Hormone evaluation included serum concentrations of thyrotrophin, free or total thyroxine (T4) and free or total testosterone. GH deficiency was confirmed after insulin-hypoglycaemia (95.7%) or another test (4.3%), with patients on stable substitution for other pituitary hormone deficiencies. Serum IGF-I samples at baseline were analysed by a competitive radioimmunoassay (RIA). Serum IGF binding protein (IGFBP)-3 at baseline was measured by an enzyme-linked immunosorbent assay (ELISA) developed by Diagnostic System Laboratories Inc. (Webster, TX, USA). Both measurements were centralized in Pharmacia & Upjohn Laboratories – Peptide Hormones, Stockholm, Sweden. Patients were studied at baseline and at 12 months for blood analysis, electrolytes, general biochemistry with a lipid profile (total cholesterol, triglycerides, low and high density lipoprotein (LDL and HDL) cholesterol), liver and kidney function measured by standard techniques.
annual cost of disease by measuring direct and indirect costs (20, 21). The patients kept a diary to indicate all health care-related visits, days off from work and medication taken. We considered hypothalamic–pituitary disease as a whole because of the difficulty in separating isolated GH deficiency. Direct costs were calculated by adding the drug cost to the retail prices (hormone substitution: thyroxine, hydrocortisone acetate, gonadal steroids and antidiuretic hormone and other concomitant therapies) including taxes to the direct medical costs associated with the direct provision of health-care services (physician services and hospitalizations). Accepting that the salary received by the worker is a good indicator of the value of lost production due to disability through illness, we transformed the days on leave into monetary units. Indirect costs were associated with loss of productivity, earnings lost from days off from work, calculated by the Spanish mean employee earnings (40.9 US dollars (USD)/day) (figures from the Spanish Ministry of Labour and Health Service) adjusted by unemployment data (National Statistics Institute Survey of active population) which was 22.8% during the study period (31.6 USD/day). Annual patient costs were used to estimate the economic impact of the disease according to prevalence. The ‘bottom-up’ approach was used for health–economic evaluation and forms a base for disease cost calculation. It studies the consumption of resources employed during the study period of a specified number of patients. The mean health cost is multiplied by the estimated prevalence. Results were compared with the health costs of the Spanish general population adjusted to 1993 data according to the retail price index (RPI) (22). The most important variables for economic evaluation in chronic diseases are age and evolution time; thus, both were considered in the study (23, 24). Non-medical and intangible costs were not evaluated.

Data analysis

Data were analysed with SPSS for Windows and/or CIA (confidence interval analysis; M J Gardner and British Medical Journal version 1.0, 1989). Comparison between groups (groups defined by variables such as sex, age or type of hormone deficiency) was made for qualitative variables by a \( \chi^2 \) test, for continuous variables which satisfy parametric test application conditions by Student’s \( t \)-test, and for non-parametric variables the Mann-Whitney U test was used. Relationships between two quantitative variables were analysed by Pearson’s or Spearman’s correlation coefficient, depending on the variable nature. Quantitative dichotomy variables were compared by McNemar’s test. Comparisons between ODA patients and the normal population from the CIRES survey was tested using 95% confidence interval (CI) for difference in proportion tests. Other CI referred to in the text are also 95%. Significance was established in a two-sided test set to the 0.05 level.

Results

Cross-sectional study

Demographic data are shown in Table 1. Aetiology of hypopituitarism was: non-functional pituitary tumour in 39.4% and functional pituitary tumour in 21.3%; non-pituitary tumour: craniopharyngioma 11.2%, meningoima 1.4% and others 2.7%; Sheehan’s syndrome represented 10.0%, empty sella 5.2% and other causes 8.8% of the total 926 patients. GH peak concentrations between 3–5 ng/ml were found in 7.9% and below 3 ng/ml in the rest. Patients with GHD with one additional pituitary hormone deficiency represented 13.4%, with two additional pituitary hormone deficiencies 23.0% and panhypopituitary patients comprised 63.6%. Diabetes insipidus was diagnosed in 30.0%. The majority of these patients with pituitary tumours had received both surgery and radiotherapy for their treatment (40.8%), surgery alone was applied in 29.1% and other treatments in 30.1% of patients. Mean evolution time of GH deficiency was 8.7 years (SD = 6.8; range: 1–34 years). Deaths registered in 34 clinical records were due to the following causes: cardiovascular disease (stroke, pulmonary thrombo-embolism and coronary disease) in 15 patients (44.1%), malignant diseases in 7 (20.6%) and other causes in 12 (35.3%).

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Cross-sectional Women</th>
<th>Longitudinal Women</th>
<th>P</th>
<th>Cross-sectional Men</th>
<th>Longitudinal Men</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cross-sectional study</td>
<td>Longitudinal study</td>
<td></td>
<td>Cross-sectional study</td>
<td>Longitudinal study</td>
<td></td>
</tr>
<tr>
<td>&lt; 35 years</td>
<td>10.2%</td>
<td>9.6%</td>
<td>ns</td>
<td>16.9%</td>
<td>16.1%</td>
<td>ns</td>
</tr>
<tr>
<td>35–50 years</td>
<td>30.7%</td>
<td>26.9%</td>
<td>ns</td>
<td>24.6%</td>
<td>30.8%</td>
<td>ns</td>
</tr>
<tr>
<td>50–60 years</td>
<td>31.9%</td>
<td>39%</td>
<td>ns</td>
<td>36.8%</td>
<td>41.7%</td>
<td>ns</td>
</tr>
<tr>
<td>&gt; 65 years</td>
<td>27.1%</td>
<td>24.4%</td>
<td>ns</td>
<td>21.6%</td>
<td>11.4%</td>
<td>ns</td>
</tr>
<tr>
<td>Number</td>
<td>485 (52.4%)</td>
<td>201 (56.5%)</td>
<td>ns</td>
<td>441 (47.6%)</td>
<td>155 (43.5%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Longitudinal study

Demographic data are shown in Table 1. Aetiology of hypopituitarism was: non-functional pituitary tumour...
in 35.4% and functional pituitary tumour in 19.4%; non-pituitary tumour: craniopharyngioma 10.4%, meningioma 0.6% and others 2.0%; Sheehan’s syndrome represented 14.3%, empty sella 6.9% and other causes 11.0% of the total 356 patients. GH peak concentrations were between 3–5 ng/ml in 5.9% and below 3 ng/ml in the rest. No significant differences were observed between patients of retrospective and prospective studies, except for other aetiologies (P < 0.05).

Mean IGF-I values expressed in standard deviation scores (SDS) ranged from $-6.9$ to $-2.9$ and mean SDS of IGFBP-3 measurements from $-1.9$ to $-1.0$ compared with a reference population (25). GHD patients with one additional pituitary hormone deficiency comprised 9.1%, two additional pituitary hormone deficiencies 21.9%, and panhypopituitarism was diagnosed in 69.0%. Treatments received for pituitary tumours were similar to those of the retrospective study: radiotherapy and surgery in 41.0%, surgery alone in 29.3% and other treatments in 29.7%. Mean evolution time of GH deficiency was 8.2 years (S.D. = 6.6; range: 2–35 years). Physical examination data and cardiovascular risk factors of 356 patients at baseline and of 320 patients followed to the 12-month visit are shown in Tables 2–4.

### Laboratory evaluation
Mean complete blood analysis, electrolytes, general biochemistry and liver and kidney function were normal at baseline and at the 12-month visit (data not shown). Percentages of patients with cardiovascular risk factors not treated with lipid-lowering drugs are shown in Table 4. Patients on lipid-lowering drug treatment increased from 11.7% at baseline to 17.3% at 12 months. Mean hormone values (free and total T4 and testosterone) demonstrated adequate standard hormonal substitution (data not shown).

### Health-related quality of life
QoL-AGHDA scores for patients at baseline were 9.4 (CI = 8.4–10.4) and at 12 months 4.8.

#### Table 2  Physical examination. Longitudinal study.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 201)</th>
<th>12 months (n = 181)</th>
<th>P</th>
<th>Baseline (n = 155)</th>
<th>12 months (n = 139)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>70.4 (12.6)</td>
<td>77.6 (15.3)</td>
<td>ns</td>
<td>83.1 (14.7)</td>
<td>78.4 (16.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>154.9 (7.1)</td>
<td>–</td>
<td>–</td>
<td>168.0 (7.8)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.3 (5.1)</td>
<td>30.3 (6.2)</td>
<td>ns</td>
<td>29.0 (4.2)</td>
<td>29.8 (4.5)</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>20.8</td>
<td>17.8</td>
<td>ns</td>
<td>13.5</td>
<td>8.0</td>
<td>ns</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>38.3</td>
<td>35.0</td>
<td>ns</td>
<td>52.3</td>
<td>49.6</td>
<td>ns</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>41.0</td>
<td>48.0</td>
<td>ns</td>
<td>34.2</td>
<td>41.4</td>
<td>ns</td>
</tr>
<tr>
<td>Waist/hip ratio (X (s.d.))</td>
<td>0.9 (0.1)</td>
<td>0.9 (0.1)</td>
<td>ns</td>
<td>1.0 (0.1)</td>
<td>0.9 (0.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (X (s.d.))</td>
<td>130.7 (23.9)</td>
<td>130.9 (22.2)</td>
<td>ns</td>
<td>126.7 (20.3)</td>
<td>127.4 (18.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic (X (s.d.))</td>
<td>79.1 (13.1)</td>
<td>80.1 (12.3)</td>
<td>ns</td>
<td>79.1 (12.0)</td>
<td>80.7 (10.6)</td>
<td>ns</td>
</tr>
</tbody>
</table>

The data of patients used for baseline and 12-months values were not significantly different.

#### Table 3  Cardiovascular risk factors I (percentage).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥ 30 kg/m²</td>
<td>M</td>
<td>34.2</td>
<td>41.4</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>41.0</td>
<td>48.0</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>M &gt; 1</td>
<td>30.0</td>
<td>25.4</td>
</tr>
<tr>
<td></td>
<td>F &gt; 0.9</td>
<td>36.2</td>
<td>34.0</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>M</td>
<td>22.6</td>
<td>23.2</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>21.7</td>
<td>24.2</td>
</tr>
</tbody>
</table>

* Hypertension was considered in patients on antihypertensive treatment at baseline and at 12 months or with blood pressure values above 140 mmHg systolic and 90 mmHg diastolic (40). The overall prevalence of hypertension in the Spanish population calculated in a sample of 29 929 subjects aged between 15–74 was 14.8% (CI: 13.3–16.2%: 16.5% for men (CI: 14.2–18.9%) and 13.2% for women (CI: 11.2–15.2%)) (32). The overall prevalence of obesity (BMI ≥ 30 kg/m²) was studied in a sample of 5388 subjects between 25–60 years of age representative of different autonomous regions in Spain: 11.5% in men and 15.2% in women. In the 45–54 age group, the prevalence in men was 16.6% (CI: 13.0–20.1%) and in women 25.9% (CI: 22.2%–29.5%) (31).
months were 10.0 (CI = 8.8–11.0). These scores were adjusted for age and education level for comparison with the reference population scores (5.49; CI = 5.27–5.71); differences were highly statistically significant ($P < 0.01$) (26).

**Health status evaluation**
Health status evaluation in the last year showed that GHD patients presented more non-specific joint aches and pains (44.4 vs 31.4%; CI: 7.1–18.9%), nerves/depression (25.9 vs 16.4%; CI: 4.4–14.6%) and high blood pressure (22.6 vs 14.9%; CI: 2.8–12.6%) than the general population, together with more hypercholesterolaemia (33.2% vs 18%; CI: 19.4–29.9%) and diabetes mellitus (9.7 vs 3.6%; CI: 2.8–9.4%). Surprisingly, varicose veins (17.1 vs 8.1%; CI: 4.7–13.3%), haemorrhoids (23.5 vs 6.4%; CI: 12.4–21.8%) and constipation (32.1 vs 6.5%; CI: 2.0–30.7%) were also mentioned more often by GHD patients. In contrast, patients did not present headaches more often than the general population (33.8 vs 30.4%; not significant (ns)). No statistically significant differences were observed in baseline-referred health status compared with that at 12 months in the patient group.

In relation to health habits, there were fewer smokers among patients (27.0% vs 34.9%; CI: 2.0–12.9%). The range of education level was: no studies (38.1%), primary education (31.8%), secondary education (19.6%) and higher education/university (10.4%). Percentages for the reference population were 3.9%, 45.1%, 38.6% and 12.4%, respectively, with statistically significant differences (26). A greater degree of social isolation was not detected in our patient group.

**Health–economic evaluation**
Direct costs were 1089.7 USD/year/patient (Table 5) and mean indirect costs 651.2 USD/year/patient (Table 6). Estimated prevalence of the disease is 1/10 000 (27); thus, 3862 individuals could be affected in Spain with a population of 38.6 million according to the 1991 census. The total direct health costs of adult hypopituitary patients

### Table 4 Cardiovascular risk factors II (percentage).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 months</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex</td>
<td>X (S.D.)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol &gt; 6.5 mmol/l</td>
<td>F 31.6</td>
<td>7.3 (0.1)</td>
<td>22.3</td>
</tr>
<tr>
<td></td>
<td>M 26.5</td>
<td>7.3 (0.1)</td>
<td>18.5</td>
</tr>
<tr>
<td>HDL cholesterol &lt; 0.9 mmol/l</td>
<td>F 37.5</td>
<td>0.9 (0.0)</td>
<td>29.2</td>
</tr>
<tr>
<td></td>
<td>M 26.1</td>
<td>0.7 (0.0)</td>
<td>24.0</td>
</tr>
<tr>
<td>LDL cholesterol &gt; 4.0 mmol/l</td>
<td>F 36.1</td>
<td>4.8 (0.1)</td>
<td>31.9</td>
</tr>
<tr>
<td></td>
<td>M 42.4</td>
<td>4.7 (0.0)</td>
<td>42.1</td>
</tr>
<tr>
<td>Triglycerides &gt; 2.3 mmol/l</td>
<td>F 19.0</td>
<td>4.2 (0.6)</td>
<td>16.4</td>
</tr>
<tr>
<td></td>
<td>M 22.9</td>
<td>3.7 (0.2)</td>
<td>20.2</td>
</tr>
</tbody>
</table>

Lipid values were taken from non-treated patients. Percentages of patients on lipid-lowering drug treatment were 11.7% at baseline and 17.3% at 12 months. Values of triglycerides, LDL and total cholesterol were statistically higher ($P < 0.01$) compared with those of a reference population composed of 133 women and 104 men aged between 50–64. Hypercholesterolaemia was present in 18% of this reference population (32).

### Table 5 Comparison of direct health costs between the general Spanish population and Spanish hypopituitary patients with GH deficiency.

<table>
<thead>
<tr>
<th></th>
<th>Annual hypopituitary patient individual health costs (USD) Present study</th>
<th>Annual hypopituitary individual health costs (USD)*</th>
<th>Total annual hypopituitary patient health costs (USD)*</th>
<th>Annual individual Spanish health costs: 1993 figures (USD)</th>
<th>Total annual Spanish health costs: 1993 figures (MUSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician services</td>
<td>41.6</td>
<td>36.6</td>
<td>141 349</td>
<td>222.2</td>
<td>8581.3</td>
</tr>
<tr>
<td>Hospital attendance</td>
<td>494.9</td>
<td>435.6</td>
<td>1 682 287</td>
<td>345.9</td>
<td>13 358.6</td>
</tr>
<tr>
<td>(out-patients included)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substitution (49%)</td>
<td>271.1</td>
<td>238.5</td>
<td>921 087</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Concomitant (51%)</td>
<td>282.1</td>
<td>248.3</td>
<td>958 935</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>553.2</td>
<td>486.8</td>
<td>1 880 022</td>
<td>143.2</td>
<td>5530.4</td>
</tr>
<tr>
<td>Total</td>
<td>1089.7</td>
<td>959.0</td>
<td>3 703 658</td>
<td>711.3</td>
<td>27 470.3</td>
</tr>
</tbody>
</table>

* For comparison, direct health costs of hypopituitary patients of the present study were adjusted according to the 1993 RPI available figures. The total Spanish population was 38.6 millions, and the estimated prevalence of GHD in adults is 1/10 000 (27).
adjusted to 1993 data were 3.7 million USD (MUSD), a small contribution to the total Spanish direct health costs of 27 470.3 MUSD (Table 5). However, when direct patient costs (expenses adjusted for comparison with available data of 1993) were compared with individuals of the general population, 35% more costs were observed (959.0 vs 711.3 USD) in patients than in the general population individuals, due mainly to drug therapies (Table 5). The Spanish total indirect costs/year are 53 304.4 MUSD (22) and the disease contributes 2.5 MUSD/year (considering the estimated prevalence of 3862 individuals). Indirect costs (loss of productivity) when distributed by evolution time showed a decrease from the early years to ten years when a slight increase was observed (Table 6). The global estimated cost of the disease (direct and indirect costs) is 6.2 MUSD/year.

Thirty-seven patients were lost during follow-up: 4 were included in a clinical trial with GH, 5 did not comply with the protocol, 1 suffered a stroke with haemiplegia, 19 missed the control visit but were checked as alive, and 8 (2.2%) died during the observation period – 3 from cardiovascular disease, 3 from malignant disease (44%) and 2 from other causes (sepsis and encephalitis).

**Discussion**

To our knowledge, this cross-sectional study is the largest (926 patients) conducted in GH-deficient adult patients. Demographic, aetiologic and clinical features of other studies are confirmed (7, 9, 13, 27–29). Cardiovascular disease has been reported to be the main cause of increased mortality in patients with hypothyroidism–pituitary disease (28). This study is not an epidemiological one on mortality, but does permit us to compare the causes of death among these patients and the general population. The death rate from cardiovascular disease in the Spanish census was 23% for the same age (30), lower, therefore, than the 44% found in patients in the prospective study.

Since statistical comparison of demographic, aetiologic and analytical data is similar between cross-sectional and longitudinal study patients, it may be assumed that results of longitudinal follow-up can be applied to the sample as a whole. The diagnosis of GH deficiency in the 926 patients is corroborated by both lack of response to GH stimulation test (< 3 ng/ml in more than 93% of patients and below 5 ng/ml in the rest) and another associated pituitary hormone deficiency. Abnormally low IGF-I and IGFBP-3 levels obtained in the group of patients followed longitudinally confirms GH deficiency. Standard substitution of other pituitary hormone deficiencies demonstrated by clinical and laboratory controls permits us to assume that abnormal findings in these patients are attributed mainly to GH deficiency. Obesity (BMI ≥ 30 kg/m²) was present in 41.0% of women and 34.2% of men in the present study, clearly higher compared with 25.9% and 16.6%, respectively, of the Spanish population at the same age (31, 32). This degree of obesity is maintained at 12 months of follow-up. Obesity in these patients was of the central type, a well-known risk factor for cardiovascular disease. Waist-hip ratio was > 1 in 30% of the men and > 0.9 in 36% of the women.

The prevalence of hypertension, a further risk factor, is somewhat higher in our patients, 22.6% in men and 21.7% in women vs 14.9% in our reference population, which ranges from 12.2 to 16.2% (32, 33). Patients of the study not treated with lipid-lowering drugs presented higher total and LDL cholesterol and lower HDL cholesterol levels compared with the reference population; these were maintained throughout the study, albeit with a slight tendency to decrease, since the percentage of patients under treatment increased in the follow-up visit. These findings of an increase in cardiovascular risk factors confirm those of other authors (13, 29).

GH-deficient adult patients had previously proved to have an HRQoL below that of the reference population, assessed by generic (7–9, 34–38) and specific (26) tests. In the present study, QoL-AGHDA and direct questioning about perceived health confirm that these GH-deficient patients have worse HRQoL and, at the same time, report greater problems of non-specific aches and pains, nerves/depression and diabetes mellitus than the reference population. Furthermore, the laboratory and physical data collected in the study corroborate that these patients also present greater problems of hypertension and dyslipaemia. Despite a history of hypopituitary

**Table 6** Indirect health costs. Annual days of sick leave of Spanish hypopituitary patients with GH deficiency.

<table>
<thead>
<tr>
<th>Years from diagnosis and number of patients</th>
<th>Days off from work</th>
<th>Mean day earnings (31.6 USD)*</th>
<th>Median days off from work per patient</th>
<th>USD/year per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4 (n = 127)</td>
<td>4294</td>
<td>135690</td>
<td>37</td>
<td>1067.8</td>
</tr>
<tr>
<td>5–9 (n = 102)</td>
<td>985</td>
<td>31126</td>
<td>9</td>
<td>305.0</td>
</tr>
<tr>
<td>10–14 (n = 46)</td>
<td>741</td>
<td>23416</td>
<td>17</td>
<td>520.0</td>
</tr>
<tr>
<td>&gt;14 (n = 46)</td>
<td>578</td>
<td>18265</td>
<td>13</td>
<td>396.9</td>
</tr>
<tr>
<td>Total (n = 320)</td>
<td>6598</td>
<td>208497</td>
<td>21</td>
<td>Mean: 651.2</td>
</tr>
</tbody>
</table>

* Mean day earnings of the present study were adjusted to 1993 figures according to the RPI and unemployment data (40.9 USD/day is transformed to 31.6 USD/day).
disease and its treatment, and conversely to what one would expect, the patients do not present a higher prevalence of headaches than the reference population. Neither do they present greater impaired social status (i.e. income, permanent job, etc.), as described by other authors, which may be explained by the fact that these patients acquired the deficiency in adulthood (12, 39).

One aspect which, to date, has not received much attention in these patients is the economic consequences of their disease. The cost of one specific disease in relation to its prevalence takes into account all the existing cases during a certain time period, normally one year, and extrapolating the costs generated by the patients sample followed to the estimated prevalence. Calculation of direct and indirect costs of these patients over one year constitutes a good approach to the economic impact that may be generated by their disease, although it could be argued that cost-of-illness calculations are seriously deficient in not including intangible costs (21). The contribution of this condition represents a small part of the direct costs of the overall Spanish Health Service expenditure. When the health costs per person are compared, it can be seen that the patients account for 35% more than the national average. The type of care in which the difference is most significant is pharmacology in which the national average expenditure per person is more than tripled. On the other hand, where out-patient care is concerned, their consumption is much lower than the national average, possibly due to the fact that follow-up of this kind of patient is principally carried out in a hospital setting. In comparison to another pharmaco-economic study conducted in Sweden on the same type of patient, the cost was somewhat higher (15), although calculations of direct costs in that study may have included the cost of the first year (surgery and/or radiotherapy) which we did not include as we followed patients with GHD for more than one year, but an increase in direct costs was seen in our study of patients compared with the general population.

The loss of productivity is not an ideal pharmaco-economic approach and has been widely criticized because it does not include the impact of collective groups such as pensioners that are not integrated in the labour market. Neither is it valid in societies with high unemployment rates, such as ours. In the present study, calculation of costs was adjusted to the unemployment rate published. The contribution of the study patients to the Spanish total indirect health costs is low and, in contrast to other chronic diseases, is higher in the first years after diagnosis, which could be interpreted as adaptation to the disease. When the disease prevalence is considered (27) and extrapolated to the total prevalence in Spain, the overall estimated cost is 6.2 million dollars; this cost is approximate since intangible costs and premature mortality were not evaluated.

Eight of the three hundred and fifty-six patients died during follow-up, which represents a 2.6-fold increase in expected mortality of the general population: 850/100,000 inhabitants (2.2% vs 0.85%) (30). Three died from cardiovascular disease, which indicates a higher incidence, with data similar to those found in the retrospective study when compared with the general population.

In conclusion, this study confirms that GH deficiency acquired in adulthood in a large population in Spain presented demographic, aetiological, clinical and laboratory characteristics similar to those found in other countries. Similarly, the higher incidence of both risk factors and cardiovascular mortality in this group of patients compared with the general Spanish population is confirmed.

Further long-term studies are required to confirm the risk of cardiovascular mortality and the influence of GH treatment on its future prevention. Understanding of the economic cost of hypothalamic–pituitary disease in adults with untreated GH deficiency is essential for posterior comparison with that of other chronic diseases and will permit future assessment of the cost–benefit ratio of substitution GH therapy in these patients.

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