Sheehan’s syndrome: baseline characteristics and effect of 2 years of growth hormone replacement therapy in 91 patients in KIMS – Pfizer International Metabolic Database

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Abstract

Objective: Sheehan’s syndrome occurs as a result of ischaemic pituitary necrosis due to severe postpartum haemorrhage. It is one of the most important causes of hypopituitarism, and hence growth hormone deficiency (GHD), in developing countries. However, little is known about the effects of growth hormone (GH) replacement therapy in patients with Sheehan’s syndrome.

Design: The demographic background characteristics of 91 GH-deficient patients with Sheehan’s syndrome (mean age ± S.D., 46.3 ± 9.4 years) were compared with those of a group of 156 GH-deficient women (mean age ± S.D., 51.5 ± 13.1 years) with a non-functional pituitary adenoma (NFPA). The baseline characteristics and the effects of 2 years of GH replacement therapy were also studied in the 91 patients with Sheehan’s syndrome and an age-matched group of 100 women with NFPA (mean age ± S.D. 44.5 ± 10.2 years).

Results: All patients were enrolled in KIMS (Pfizer International Metabolic Database). Patients with Sheehan’s syndrome were significantly younger at pituitary disorder onset, diagnosis of GHD and at entry into KIMS than patients with NFPA ($P < 0.01$), and had significantly lower insulin-like growth factor I levels ($P < 0.001$). At baseline, quality of life (QoL) was significantly ($P < 0.05$) reduced in patients with Sheehan’s syndrome compared with those with NFPA ($P < 0.001$). With regard to treatment effects, lean body mass increased significantly ($P < 0.05$), QoL improved significantly ($P < 0.05$) and total and low-density lipoprotein-cholesterol decreased significantly ($P < 0.05$) in patients with Sheehan’s syndrome after 1 year of GH replacement therapy. Similar significant changes in QoL and lipid profiles occurred in patients with NFPA after 2 years of GH replacement. Blood pressure remained unchanged in patients with Sheehan’s syndrome, but decreased significantly ($P < 0.01$) in the group with NFPA after 1 year, before returning to pretreatment levels at 2 years.

Conclusions: In conclusion, patients with Sheehan’s syndrome have more severe GHD compared with individuals with NFPA. GH replacement therapy in patients with Sheehan’s syndrome may have beneficial effects on QoL, body composition and lipid profile.

Introduction

Patients with hypopituitarism of different aetiologies have increased mortality compared with age-matched controls (1–3). In a study of 1034 hypopituitary adults, growth hormone deficiency (GHD) was shown to be associated with an increased prevalence of cardiovascular risk factors and fractures, as well as an impaired quality of life (QoL) (4). Other signs and symptoms include abnormal body composition (reduced lean body mass and increased abdominal adiposity), reduced strength and exercise capacity, impaired psychological well-being, reduced muscle strength, elevated serum lipids, reduced bone mineral density and excess weight (5).

Sheehan’s syndrome, which was originally described by Sheehan in 1937, occurs as a result of ischaemic pituitary necrosis due to severe postpartum haemorrhage (6). The prevalence of Sheehan’s syndrome in 1965 was estimated to be 100–200 per 1000000 women (7). Now, however, it is a rare cause of hypopituitarism in developed countries. Abs et al. (4), in their study of 1034 hypopituitary adults, reported that Sheehan’s syndrome was the sixth most frequent cause of GHD, being responsible for 3.1% of cases, compared with 53.9% due to a pituitary tumour. Only one
case was reported in a database of 404 patients with pituitary disease in the United Kingdom (8), and it was not listed as a cause of hypopituitarism in 333 patients in Sweden studied by Rosén and Bengtsson (1). Although the syndrome is currently much less common than previously because of marked improvements in obstetric care in developed countries, it is still an important cause of hypopituitarism in developing countries.

We have previously reported that 56.2% of patients with Sheehan’s syndrome had panhypopituitarism and 43.8% had selective pituitary insufficiency; all the patients had GHD (9). As growth hormone (GH)-secreting cells are situated in the lower and lateral regions of the pituitary gland and are most likely to be damaged by ischaemic necrosis, it is not surprising that GH is one of the first hormones to be lost. Haddock et al. (10) evaluated 50 patients with Sheehan’s syndrome and found that 84% had panhypopituitarism, while 14% had selective pituitary deficiencies. Only one patient had a normal GH reserve. Rabkin and Frantz (11) evaluated pituitary function in 25 adults with evidence of hypopituitarism, one of whom had Sheehan’s syndrome and one who probably had Sheehan’s syndrome. All patients exhibited a significant defect in GH secretion, as measured by an insulin tolerance test (ITT). The order of frequency of hormonal loss was GH, gonadotrophins, adrenocorticotrophin and thyrotrophin.

Patients with hypopituitarism and GHD associated with Sheehan’s syndrome tend to acquire their disease at a much earlier age and, as a consequence, to be diagnosed and treated earlier than patients with adult-onset GHD of other aetiologies. The present study set out to compare the demographic baseline characteristics of patients with Sheehan’s syndrome and GH-deficient women with a non-functioning pituitary adenoma (NFPA) in KIMS (Pfizer International Metabolic Database). Secondly, baseline characteristics and the effects of 2 years of GH replacement therapy were studied in the patients with Sheehan’s syndrome and in an age-matched group of women with NFPA.

### Materials and methods

The present study was performed in two parts. In the first part, the demographic background characteristics of 91 GH-deficient patients with Sheehan’s syndrome (mean age±s.d., 46.3±9.4 years) were compared with those of 156 non-irradiated women with GHD due to an NFPA (mean age±s.d., 51.5±13.1 years). In the second part of the study, the effects of 1 and 2 years of GH replacement therapy were studied in 100 age-matched women with NFPA (mean age, 44.5±10.2 years) and the 91 patients with Sheehan’s syndrome. All patients were included in KIMS, which is the largest pharmacoepidemiological survey of the use of GH replacement therapy in adults. KIMS was launched in 1994 and, to date, contains information on 9000 patients from 28 countries. The countries of origin of the patients in this analysis are given in Table 1. All patients gave their informed consent for the study, which was approved by the ethics committee at each hospital.

#### Design of the KIMS surveillance programme

Following enrolment, each patient visits his or her local clinic at a frequency determined by the treating physician; however, a minimum of one visit per year is recommended. Data are collected at each clinic visit on specially designed case report forms, and are entered into a central database. This data collection process is monitored according to good clinical practice guidelines.

#### Assessment of patient characteristics

All the patients had a full history taken and a physical examination, and were receiving standard hormone replacement therapy for any combination of secondary adrenal, gonadal and thyroid failure as well as diabetes insipidus. For all patients the age of onset of the pituitary disorder and details about the diagnosis of GHD were noted on enrolment into KIMS, and the following variables recorded: age, body weight, body mass index (BMI), waist:hip ratio, duration of GH therapy, number of additional pituitary hormone deficiencies and serum levels of insulin-like growth factor I (IGF-I), total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides. The IGF-I and lipid profiles were analysed centrally. Serum concentrations of IGF-I

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**Table 1** Countries of origin of the patients with Sheehan’s syndrome and those with non-functional pituitary adenoma (NFPA).

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of patients with Sheehan’s syndrome</th>
<th>Number of patients with NFPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Australia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Austria</td>
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<td>5</td>
</tr>
<tr>
<td>Belgium</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Denmark</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>France</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Germany</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>Greece</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Ireland</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Italy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Korea</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Spain</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Sweden</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Switzerland</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Taiwan</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>UK</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>USA</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

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were determined by radioimmunoassay after separation of IGFs from IGF-binding proteins (IGFBPs) by acid–
ethanol extraction and with des(1–3)-IGF-I as radioligand, to minimize interference of IGFBPs in the extract. The intra- and interassay coefficients of variation were 10% and 3.1% respectively. The normal range in the IGF-I assay was adjusted for age and is expressed as IGF-I standard deviation scores (SDS). The GH concentrations were determined by different methods in each hospital.

Lean body mass and fat mass were calculated using bioelectrical impedance analysis (BIA) or dual-energy X-ray absorptiometry (DXA). Waist and hip measurements were performed according to KIMS guidelines. Blood pressure was measured in the supine position after 5 min of rest.

The ITT was used to diagnose GHD in the majority of patients with Sheehan’s syndrome and NFP A (n = 50 and 84 respectively). Other standard GH stimulation tests used included arginine, glucagon and GH-releasing hormone. The criterion for entry of patients into the study was a GH peak response of less than 3 μg/l after the ITT or other standard stimulation tests, performed as part of the patient’s anterior pituitary function tests. Hormonal evaluation included the study of thyrotrophin and adrenocorticotropic secretion, the gonadal axis and arginine–vasopressin secretion in all cases. Of the 191 matched patients studied, 27 (16 with Sheehan’s syndrome and 11 with NFP A) had been treated with GH before enrolment into KIMS; however, none of them had received GH replacement during the 6 months preceding entry into KIMS. These patients are referred to as the semi-naïve group. In the remaining 164 patients (75 with Sheehan’s syndrome and 89 with NFP A), GH treatment was initiated at the time of enrolment. These are referred to as the naïve group. The patients were treated with GH (Genotropin; Pfizer, Stockholm, Sweden) using an automated pen-injection device (KabiPen, Genotropin Pen; Pfizer) and followed for 2 years. The mean (±S.D.) starting doses in the patients with Sheehan’s syndrome and those with NFP A were 0.27±0.17 and 0.26±0.16 mg/day (0.79±0.50 and 0.78±0.48 IU/day) respectively.

QoL was assessed using the disease-specific QoL Assessment of GHD in Adults (QoL-AGHDA) questionnaire (12) before treatment and after 1 and 2 years of treatment with GH.

Statistical analysis
Results are expressed as means±S.D., median with 10th–90th percentiles, or as a percentage. The Kolmogorov–Smirnov test was applied to check the normality of the variables. Student’s t-test was used to compare normally distributed variables, and the Wilcoxon rank–sum test was used for non-normally distributed variables. Significance was established in a two-sided test set to the 0.05 level.

Results
Background characteristics
The background characteristics of the study populations are shown in Table 2. Patients with Sheehan’s syndrome were significantly younger at onset of pituitary disorder, diagnosis of GHD and entry into KIMS (P<0.001). The time from both pituitary disorder onset and GHD diagnosis to entry into KIMS was much longer in the patients with Sheehan’s syndrome than in those with NFP A (P < 0.01, P < 0.001 respectively).

The degree of GHD was more severe in the patients with Sheehan’s syndrome, as indicated by their lower GH peaks. Although GH levels were measured at different times and in different laboratories, serum IGF-I levels were analysed centrally, and the lower IGF-I SDS in patients with Sheehan’s syndrome also indicate a greater severity of GHD. The number of additional anterior pituitary hormone deficiencies was similar between the groups (median was three for each group; Table 3). The prevalence of thyrotrophin and adrenocorticotropic deficiencies was significantly higher in those with Sheehan’s syndrome than in those with NFP A (P < 0.001 and P < 0.05 respectively).

Baseline characteristics
Baseline height, weight, BMI, waist circumference and hip circumference were significantly lower in the patients with Sheehan’s syndrome than in those with NFP A, although the waist:hip ratio was not significantly

Table 2 Background characteristics of the patients with Sheehan’s syndrome and those with non-functional pituitary adenoma (NFP A).

<table>
<thead>
<tr>
<th></th>
<th>Sheehan’s n</th>
<th>NFP A n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.3±9.4</td>
<td>51.5±13.1***</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>40.0</td>
<td>51.0†††</td>
</tr>
<tr>
<td>Age at onset of pituitary disease (years)</td>
<td>34.0</td>
<td>44.5†††</td>
</tr>
<tr>
<td>Time from diagnosis of GHD to enrolment in KIMS (years)</td>
<td>8.0</td>
<td>3.0††</td>
</tr>
<tr>
<td>Time from diagnosis of GHD to enrolment in KIMS (years)</td>
<td>8.0</td>
<td>3.0††</td>
</tr>
<tr>
<td>Median number of additional pituitary hormone deficiencies</td>
<td>3</td>
<td>91</td>
</tr>
<tr>
<td>GH peak (μg/l)</td>
<td>0.52±0.5</td>
<td>0.84±0.88**</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>−3.34</td>
<td>−2.15††</td>
</tr>
</tbody>
</table>

**P < 0.01, ***P < 0.001 compared with Sheehan’s syndrome (Student’s t-test); ††P < 0.01, †††P < 0.001 compared with Sheehan’s syndrome (Wilcoxon rank–sum test).
different between the groups. In addition, lean body mass, as assessed by BIA, was lower in the patients with Sheehan’s syndrome than in those with NFPA, as were systolic and diastolic blood pressures. Patients with Sheehan’s syndrome had a significantly higher percentage of patients with additional pituitary hormone deficiencies (Sheehan’s syndrome, 4.4%; NFPA, 5.7%) and neoplasms (Sheehan’s syndrome, 2.2%; NFPA, 2.5%) were similar in both groups before treatment with GH. Ten of the patients with Sheehan’s syndrome and 3 of those with NFPA had arterial hypertension (P < 0.05). Coronary heart disease was detected in nine of the patients in the NFPA group and in one patient with Sheehan’s syndrome.

Response to GH treatment

The starting dose in the patients with Sheehan’s syndrome was 0.27 ± 0.17 mg/day (0.79 ± 0.50 IU/day), which was titrated against the clinical response and IGF-I levels to a maintenance dose of 0.45 ± 0.28 mg/day (1.34 ± 0.84 IU/day) (P < 0.0001). The starting and maintenance doses for the NFPA patients were 0.26 ± 0.16 and 0.41 ± 0.21 mg/day (0.78 ± 0.48 and 1.22 ± 0.63 IU/day) (P < 0.0001) respectively. There were no significant changes in GH dose between 1 and 2 years of treatment.

Those variables that changed significantly after either 1 or 2 years of GH treatment are detailed in Table 4. As expected, IGF-I SDS increased markedly in both groups during GH treatment. The other major change was a significant decrease in the QoL-AGHDA score after 1 year (P < 0.05), indicating an improvement in QoL. The decrease in QoL-AGHDA score was maintained after 2 years, although the difference between the 2-year value and baseline was not statistically significant in patients with Sheehan’s syndrome.
Weight and BMI were significantly increased in the patients with Sheehan’s syndrome after two years of treatment ($P < 0.01$). Lean body mass, as measured by BIA, increased significantly in patients with Sheehan’s syndrome after 1 year ($P < 0.05$) but did not change significantly in the patients with NFP A. Basal glucose levels were significantly ($P < 0.001$) increased in the patients with Sheehan’s syndrome after 1 year of GH treatment, but returned to pretreatment levels after 2 years and did not change significantly in the patients with NFP A after either 1 or 2 years of GH treatment. The level of glycosylated haemoglobin (HbA1c) was significantly increased in the NFP A patients after 1 and 2 years of GH treatment, but returned to pretreatment levels after 2 years of GH treatment in patients with NFP A. This selection bias is a reflection of the fact that the prevalence of Sheehan’s syndrome varies among countries and is generally lower than NFP A, especially in developed countries. Nevertheless, other baseline characteristics, including IGF-I SDS, are unlikely to be affected by ethnicity, and these variables indicate a greater severity of GH deficiency in patients with Sheehan’s syndrome than in patients with NFP A.

It is well known from other studies that QoL is reduced in GH-deficient adults compared with the normal population, and some studies have reported that GH replacement in severely GH-deficient adults has beneficial effects on QoL (13–15). In the present study, the QoL of women with Sheehan’s syndrome before GH treatment in KIMS was shown to be worse than that of women with NFP A, as indicated by their significantly higher score on the QoL-AGHDA questionnaire. It is unknown whether the poorer QoL in untreated patients with Sheehan’s syndrome is due to the intrinsic nature of this form of hypopituitarism or is solely a result of the early onset and severity of GHD in these individuals. Nevertheless, QoL-AGHDA score significantly improved in both patient groups after 1 and 2 years of therapy, demonstrating the beneficial effects of GH replacement on QoL.

In this study, total cholesterol and LDL-cholesterol levels significantly decreased after 1 year of GH treatment in the patients with Sheehan’s syndrome and after 2 years of GH treatment in patients with NFP A. Non-significant decreases occurred in triglyceride levels with NFP A. Baseline height, weight, BMI, waist circumference and hip circumference were significantly lower in the patients with Sheehan’s syndrome than in those with NFP A, indicating a greater severity of GHD. This could be a result of differences in ethnicity between the two groups; for example, there were 13 patients with Sheehan’s syndrome and only two patients with NFP A from Korea, whereas 19 patients with NFP A and only eight patients with Sheehan’s syndrome were from Sweden. The selection bias is a reflection of the fact that the prevalence of Sheehan’s syndrome varies among countries and is generally lower than NFP A, especially in developed countries. Nevertheless, other baseline characteristics, including IGF-I SDS, are unlikely to be affected by ethnicity, and these variables indicate a greater severity of GH deficiency in patients with Sheehan’s syndrome than in patients with NFP A. The present study shows that women with Sheehan’s syndrome are characterized by long-term GHD. Patients are significantly younger at the onset of pituitary disease and at diagnosis of GHD, compared with women with NFP A.
levels in the patients with Sheehan’s syndrome, whereas a significant increase was observed in triglyceride levels in the women with NFP A after 2 years of GH treatment. In another study in which patients were treated with GH for 10 years, total cholesterol and triglyceride concentrations did not change in GH-treated and untreated GH-deficient adults (16). In untreated GH-deficient adults, levels of total cholesterol, LDL-cholesterol, triglycerides and apolipoprotein B have previously been shown to be increased, and HDL-cholesterol levels reduced compared with those in healthy adults (17).

Yuen et al. (18) reported that short-term (7 days) administration of the highest GH dose (0.025 mg/kg/day) induced insulin resistance, whereas the lowest dose (0.0017 mg/kg/day) could represent the optimal starting dose in GH-deficient adults due to its beneficial effects on β-cell function without compromising insulin sensitivity. The GH Research Society (19) has recommended that GH therapy in adults should start with a dose ranging from 0.15 to 0.30 mg/day (0.45 to 0.90 IU/day). In the present study the mean (±S.D.) starting doses in the patients with Sheehan’s syndrome and NFP A were 0.28±0.17 and 0.27±0.16 mg/day (0.84±0.53 and 0.81±0.50 IU/kg/week) respectively. We found that basal glucose levels significantly increased after 1 year of treatment but had returned to pretreatment levels after 2 years of treatment. HbA1c levels did not change in the patients with Sheehan’s syndrome, but significantly increased in NFP A patients after both one and two years of GH treatment. More studies are needed to clarify the relationship between GH treatment and glucose metabolism.

The median waist circumference before treatment with GH was significantly smaller in patients with Sheehan’s syndrome than in those with NFP A. However, GH treatment did not significantly reduce the waist circumference or the waist:hip ratio in either group after 1 or two years of GH treatment. In contrast, Drake et al. (20) found that the mean waist circumference and the waist:hip ratio in GH-deficient men and women fell significantly after 6 months of GH treatment and remained decreased after 12 months. In the present study, lean body mass was significantly lower at baseline in the patients with Sheehan’s syndrome than in those with NFP A, and was significantly increased only in the patients with Sheehan’s syndrome after 1 year of GH treatment.

Central diabetes insipidus has been described as part of Sheehan’s syndrome (21–23), although this is rare. Arnaout and Ajjouni (24) demonstrated impaired osmoregulation of vasopressin secretion in 12 of 15 patients with Sheehan’s syndrome. None of the studied patients developed permanent diabetes insipidus.

Basal systolic and diastolic blood pressures were significantly lower in the patients with Sheehan’s syndrome than in those with NFP A. There was no change in either systolic or diastolic blood pressures after GH treatment in the women with Sheehan’s syndrome. In contrast, GH treatment in the women with NFP A resulted in significantly decreased systolic and diastolic blood pressure after 1 year. Some studies have shown that GH replacement therapy reduces diastolic blood pressure (25, 26), whereas another has shown no effect (27), and Gibney et al. (16) observed no change in either systolic or diastolic blood pressure in ten GH-deficient adults treated with GH for 10 years.

This study has compared the baseline characteristics of patients in KIMS with Sheehan’s syndrome with those of patients with an NFP A, and has examined the effects of 2 years of GH replacement therapy in these groups of patients. No direct comparisons have been made between the groups after GH replacement therapy commenced; however, the beneficial effects of GH replacement therapy on QoL, IGF-I levels, serum lipid profiles and body composition have been demonstrated in both groups of patients.

In conclusion, Sheehan’s syndrome, which is a common cause of hypopituitarism in developing countries, is characterized by long-lasting GHD, which appears to be more severe than that seen in adults with NFP A and results in a poorer QoL. As in other adults with GHD, GH replacement therapy in patients with Sheehan’s syndrome has beneficial effects on QoL, body composition and the lipid profile.

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References


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