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Effects of 18-month of growth hormone (GH) replacement therapy in patients with Sheehan's syndrome

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Abstract

Objective: Growth hormone deficiency (GHD) in adults is associated with abnormal body composition, altered lipid profile, reduced quality of life and osteoporosis. Replacement with recombinant GH results in significant improvements in most of these altered parameters. The most common cause of adult GHD in previous studies was due to pituitary tumors or their treatment. Sheehan's syndrome classically refers to postpartum hypopituitarism due to pituitary necrosis occurring secondary to massive bleeding at or just after delivery. While severe GHD is a well-established feature of Sheehan's syndrome, the effects of Growth hormone replacement therapy (GHRT) in these patients has not been extensively investigated. The present study was therefore designed to investigate the effects of GHD and GHRT in patients with Sheehan's syndrome.

Design: The study comprised 14 severely GH-deficient patients with Sheehan's syndrome with a mean age of 49.4 ± 7.9 yr. Treatment with GH was started at a dose of 0.15 mg per day in month 1, was increased to 0.30 mg per day in month 2, and was maintained at 0.66 mg per day until the end of month 18. With the similar maintenance dose adequate age adjusted IGF-I levels for each patient has been achieved. Blood pressure, lipid profile, biochemical parameters, anthropometric measurements including body mass index (BMI), waist and waist to hip ratio (W/H), and bone mineral density (BMD) were investigated before and at 3, 6, 12 and 18 months of the GHRT.

Results: The duration of GHD from the onset of the disease was 19.4 ± 1.6 yr. The majority of the patients (78%) had panhypopituitarism. At baseline mean total cholesterol, LDL-cholesterol and triglyceride levels were higher than the normal reference ranges but HDL-cholesterol levels were within the lower normal range. During the treatment period total cholesterol and LDL-cholesterol levels decreased and HDL-cholesterol levels increased significantly ($P < 0.05$). Waist circumference and waist to hip ratio were decreased significantly during the GHRT when compared to basal measurements ($P < 0.05$). There was a significant positive correlation between the basal waist circumference and the duration of GHD ($P < 0.05$).

Conclusions: This study clearly demonstrates that Sheehan's syndrome is characterized by severe and long-standing GHD. GHRT have beneficial effects in several parameters including lipid profile and waist circumference. But we could not observe any improvement in BMD after 18 months of GHRT. However interpretations of the present results need to be made with caution because of the uncontrolled design. Further placebo controlled studies with high number of patients with Sheehan's syndrome are warranted.

Keywords: Sheehan's syndrome; GH deficiency; GH replacement therapy; IGF-I; Bone mineral density; Lipid profile; Body composition

1. Introduction

Growth hormone deficiency (GHD) in adults has been accepted recently as a clinical entity [1]. It is associated with abnormal body composition [2–4], altered

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lipid profile with decreased high density lipoprotein (HDL) cholesterol and increased low density lipoprotein (LDL) cholesterol [5–7], and osteoporosis [8–11]. Replacement with recombinant GH results in significant improvements in body composition [2–4], lipid profile [5,12–14] and osteoporosis [9,10,15,16]. The most common causes of adult GH-deficiency are pituitary adenoma and parasellar masses or their treatment [17]. The contradictory results in different studies related to the effects of Growth hormone replacement therapy (GHRT) are probably due to the differences in the underlying diseases that cause GHD and the previous treatments. In the present study, we evaluated a homogenous group of patients who have the same aetiology of GHD.

Sheehan's syndrome which was first described by Sheehan [18] classically refers to postpartum hypopituitarism due to pituitary necrosis occurring during severe hypotension or shock secondary to massive bleeding at or just after delivery. It is still a serious health problem in some developing countries and is characterized by varying degrees of anterior pituitary dysfunction [19]. 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. GH is one of the earliest hormones lost and it was reported that GH deficiency was neither variable according to the degree of hypopituitarism nor related to the number of additional anterior pituitary hormone deficiencies in Sheehan's syndrome [20]. Sheehan's syndrome is characterized by severe and long-standing GH deficiency [19]. While GHD is a well-established feature of Sheehan's syndrome, the effects of GHRT in this patient group has not been extensively investigated.

The present study was therefore designed to investigate the effects of GHD and 18 months of GHRT on several parameters in patients with Sheehan's syndrome.

2. Subjects and methods

2.1. Study design

The study was designed as an open labeled study for 18 months and, measurements were carried out before and at 3, 6, 12 and 18 months of the GHRT. This study was approved by the Ethics Committee and the Institutional Review Board of Erciyes University Medical School, and informed consent was obtained from each patient.

GH was given according to the recommendations of the Growth Hormone Research Society Workshop [21]. GH was self-administered at night subcutaneously and drug compliance was assessed by vial count. Treatment with GH (Genotropin; Pfizer Stockholm, Sweden) was started at a dose of 0.45 IU (0.15 mg)/per day in month 1, was increased to 0.9 IU (0.30 mg)/per day in month 2, and was maintained at 2 IU (0.66 mg)/per day until the end of month 18. With the similar maintenance dose adequate age adjusted IGF-I levels for each patient have been achieved.

2.2. Patients

The study comprised 14 patients with Sheehan's syndrome, with a mean age of 49.4 ± 7.9 yr (range, 29–58) (Table 1). All of the patients received GHRT for 12 months and 10 of them received GHRT for 18 months.

Table 1
Background characteristics of the patients with Sheehan's syndrome

Patient no.	Age (yr)	Onset (yr)[a]	Duration (yr)[b]	Duration GHD (yr)[c]	Other hormones[d]	GH[e] (mIU/l)	IGF-I[f] (ng/ml)
1	50	25	16	25	G, T	0.8	17
2	52	31	16	21	G, T, A	0.3	11
3	54	37	17	17	G, T, A	0.3	18
4	54	27	16	27	G, T	0.8	9
5	35	24	6	11	G, T	0.6	18
6	57	34	11	23	G, T, A	0.7	22
7	50	28	20	22	G, T, A	0.3	12
8	58	38	17	20	G, T, A	0.6	12
9	50	36	14	14	G, T, A, ADH	1.1	41
10	48	28	15	20	G, T, A	1.3	35
11	54	28	25	26	G, T, A	1.3	14
12	50	36	6	14	G, T, A	1.2	51
13	51	27	20	24	G, T, A	1.0	25
14	29	21	8	8	G, T, A	0.3	40

[a] Onset of disease; the age at the last labor.
[b] Duration of the disease; time interval between the last labor and the diagnosis of the hypopituitarism.
[c] Duration of GHD ; time interval between the last labor and onset of the GHRT.
[d] Hormone deficiencies other than GH: G, gonadotropins; T, TSH; A, ACTH; ADH, anti diuretic hormone.
[e] Peak GH response to ITT (mIU/l).
[f] IGF-I levels (ng/ml) before GHRT.