CLINICAL STUDY

Effects of GH on cognitive function in elderly patients with adult-onset GH deficiency: a placebo-controlled 12-month study

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Abstract

Objective: Young adults with childhood-onset GH deficiency (GHD) have reduced memory and attention, which can be improved by treatment with GH. Little information is available on cognitive function in elderly GHD patients.

Design: Single center, double-blind, randomized, placebo-controlled study of 52-week duration.

Methods: Elderly GH therapy naïve GHD patients (n ≥ 34; age range 60–77 years) were enrolled and randomized to receive placebo or GH therapy which was titrated to achieve a target IGF-I level of +1 to +2 S.D. of the normal mean for age. Cognitive function was assessed at baseline and after 24 and 52 weeks, using a computerized psychometric test package (Neurobehavioral Examination System-2).

Results: The mean GH dose was 0.16 ± 0.06 mg/day; mean IGF-I increased from 135 ± 59 ng/ml at baseline to 213 ± 77 ng/ml during active treatment. The GH-treated group had better mean serial digit learning scores compared with placebo group (P < 0.05). Assessment of effect sizes showed that improvements in memory occurred with GH after 24 weeks. The overall adverse event rates were similar in the GH and the placebo group.

Conclusion: This study indicates that GH replacement may be accompanied by improvement in certain measures of cognitive function in elderly patients with GHD.

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Introduction

Organic growth hormone (GH) deficiency (GHD) in the elderly is distinct from the decline in GH secretion associated with the aging process (1). Studies have demonstrated that elderly patients with GHD are both physically and psychologically less healthy than their age-matched peers (2–4). Relatively few studies have addressed the effects of GH replacement therapy in this population. In an open-label trial, treatment with lower doses of GH (0.15 and 0.3 mg/day) in 12 patients aged 61–86 years was well tolerated, whereas 25% developed adverse effects on a higher dose (0.5 mg/day) (5). Beneficial effects on body composition and quality of life were observed after 6 months. In a 6-month placebo-controlled trial with a 12-month open-label extension period, GH therapy was found to decrease fat mass, increase in lean body mass, and transiently increase maximal exercise capacity in 31 elderly GHD patients (6, 7). Likewise, positive effects on the waist to hip ratio and the lipid profile were found after GH replacement therapy for up to 3 years (8). Recently, long-term treatment with GH was found to also improve hand and leg muscle strength in elderly GHD patients (9). Data from a larger cohort of elderly GHD patients found that patients with GHD aged > 65 years had similar baseline characteristics to younger adult GHD patients, while the effects of GH on body composition, lipids and quality of life as assessed by Adult Growth Hormone Deficiency Assessment (AGHDA) score (10) were also similar.

In younger patients with GHD, treatment with GH has been associated with either a neutral effect or improvements in measures of memory and attention. Factors associated with an improvement were the extent of cognitive impairments at baseline, the dose of GH administered and to some extent the age at onset of GHD (11). In GHD patients receiving GH, measures of cognitive functions were equivalent to those seen in matched controls (12).

In elderly healthy subjects, some aspects of cognitive function have been reported to be inversely related to serum insulin-like growth factor-I (IGF-I) (10, 13), while regional cerebral blood flow during performance of a memory task was found to increase more in elderly healthy subjects with ‘high’ circulating IGF-I levels compared with a group with ‘low’ IGF-I levels (14).

Whether replacement therapy with GH in elderly patients with GHD can modify cognitive functions
positively has not been addressed previously. In the present 12-month placebo-controlled study, we used a validated computerized battery of tests to assess cognitive and mood performance measures in older patients with adult-onset GHD who had not previously received GH therapy.

Subjects and methods

Study design

This was a single center, double-blind, randomized, placebo-controlled, parallel group study of 52-week duration. Patients were assigned randomly on a 1:1 ratio to receive either recombinant human GH (Genotropin) or placebo administered via identical cartridges. GH therapy was begun at a dose of 0.1 mg/day and was titrated in 0.1 mg/day steps every 4 weeks. The decision to increase the dose of Genotropin/placebo was dependent on the levels of IGF-I and by the absence of adverse events. The target IGF-I level was between +1 and +2 SDS of the normal mean. IGF-I levels that were +2 SDS or more above the normal mean necessitated a reduction in administered GH dose. Assessment of IGF-I levels was performed at a central laboratory; all decisions on changes in GH dose were made by an independent physician who was not involved in the clinical care of the patients. To maintain other aspects of the blinding of the study, dose adjustments in the placebo group were performed using random assignment to one of the four dose titration schedules by the independent physician. The protocol was approved by the ethics committee at the Oxford Radcliffe Hospitals NHS Trust, Oxford, UK.

Patients

Included in the study were male or female patients aged 60–80 years with adult-onset GHD of at least 24 months occurring in combination with at least one other pituitary hormone insufficiency (except prolactin). GHD and other pituitary hormonal hypofunction had to be established on the basis of an insulin tolerance test (ITT); if not tolerated, pituitary hormonal hypofunction had to be established on the basis of an arginine stimulation test. GHD was defined as a peak response latency for each of the nine items in the trial
and the number of errors (digits matched incorrectly with the test symbols).

**Pattern memory** This test measured visual memory. A pattern of filled cells in a 10 × 10 matrix was displayed for 4 s, and after a 3-s blank screen retention interval, three patterns were presented. The subject is required to select the pattern that had been presented earlier. The performance measure was the number of trials correct out of 25.

**Serial digit learning** This test measured learning and memory. A long sequence of single digits was presented one at a time, and the subject was asked to recall as many of the digits as possible. The same sequence of digits was presented again until either the subject recalled the entire sequence correctly for two trials in a row or a maximum number of trials was reached. The performance measure was the error score, i.e. the sum of errors over all the trials attempted.

**Digit span** This test measured short-term memory. A series of digits is presented, with immediate typed recall required in the original order of presentation (forward test) or in the reverse order of presentation (backward test). The sequence increased until the subject was incorrect on two consecutive trials with a given sequence length. The performance measure was the maximum number of digits recalled in the correct sequence.

**Associate learning and associate recall** These tests measured learning and intermediate memory respectively. Nine pairs of first names and respective occupations were shown for 2 s each, followed by the display of the name and all alternative occupations. Subjects were required to indicate which occupation was associated with each name. The performance measure was the sum of the correct responses across three trials with the same pairs.

**Colour word** Presentation of one of the four words: green, yellow, red, or blue. Each word was printed in the colour corresponding to the meaning of the word (i.e. the word ‘red’ printed in red) or in one of the other three colours not corresponding to the meaning of the word (i.e. the word ‘red’ printed in yellow, etc.). The subject was asked to respond to the stimuli which were shown for 2 s each to depress a key to indicate whether the meaning of the presented word corresponded to the colour of the print. The 16 possible colour–word combinations were randomly distributed within each sequence of 16 stimuli. The performance measure was the number of errors.

**The profile of mood states** This required subjects to answer a 25-item questionnaire in which they are asked to rate their level of tension, depression, anger, fatigue and confusion on a scale of 1–5 on five different items for each descriptor (17). Performance measures are the summed ratings on the five items for each mood descriptor.

**The trail making test (TMT)** TMT is given in two parts, A and B. The subject must first draw lines to connect 25 consecutively numbered circles that are arranged in a random visual array on a single sheet of paper (part A). Part B requires the subject to connect the same number of consecutively numbered and lettered circles on another worksheet by alternating between the two sequences. The sequence must follow alphanumeric order. The subject is urged to connect the circles as fast as possible without lifting the pencil from the paper. Both parts of the TMT require motor speed and coordination, attention, mental, or cognitive flexibility and are conducted under the supervision of an operator (18).

The baseline performance of the NES and TMT was compared with published norms for age (15, 19) and indicated a suboptimal cognition of the patients in the present study.

**Biochemical analyses**

At screening and again at weeks 24 and 52, patients underwent blood testing for haematology and clinical chemistry (liver and renal functions). Biochemical markers were also assessed at these time points and included serum testosterone, oestrogen, prolactin, thyroid-stimulating hormone, free T4 and T3. At randomization and again at weeks 12, 24, and 52, patients also underwent haematology and biochemical testing that included IGF-I, fasting glucose, insulin and HbA1c. For IGF-I measurements, an acid/ethanol extraction IRMA IGF-I assay from Diagnostic Systems Laboratories was used (sensitivity 0.80 ng/ml). The intra-assay coefficient of variability (CV) were the following: 3.4% at 9.4 ng/ml IGF-I, 3.0% at 55.4 ng/ml, and 1.5% at 263.6 ng/ml. The intra-assay CV values for the IGF-I assay were 8.2% at 10.4 ng/ml, 1.5% at 53.8 ng/ml and 3.7% at 255.9 ng/ml.

**Statistical analyses**

A test for treatment effect with respect to change from baseline in IGF-I was performed at 24 and 52 weeks, where the model included two factors (treatment and gender), with baseline IGF-I as a covariate. For fasting glucose, HbA1c and insulin, Van Elteren’s test was performed to evaluate a potential treatment effect with respect to change from baseline in each response at 24 and 52 weeks, stratifying for gender and baseline response. Each test utilized an individual 5% level of significance.
The performance measures from the psychometric and mood assessments were compared between the placebo and the GH groups at each time point using analysis of covariance (ANCOVA) in which baseline performance was treated as the covariate. In three cases, pre-baseline values were used to increase the sample size. Where ANCOVA was significant, the data for the assessment were compared with baseline using matched-pairs t-tests. For all performance measures, scores at each assessment were compared with baseline and expressed as an effect size. An effect was classified as being significant if the probability of occurring by chance was <0.05 (i.e. type I error rate 5%). A measure of effect size was also computed for the difference from the baseline at the 24- and 52-week assessment for each performance measure.

**Results**

**Patient population**

A total of 34 patients (22 males and 12 females) met the criteria for inclusion in the study. The mean age of the patients was 66 years (range 60–77 years). Sixteen patients (five females) were assigned to the GH arm and 18 patients (seven females) to the placebo arm. Thirty patients completed the study. One patient (female) withdrew from the trial after randomization without providing a reason for discontinuation. One patient (male) emigrated after participating in the study for 35 weeks. One patient (male) died of unrelated causes during the course of the trial period. One patient (male) withdrew from the trial due to an adverse event (liposarcoma). The patient characteristics are shown in Table 1. All patients were euthyroid during the study duration. Men with gonadal hormone insufficiency were on replacement therapy with testosterone, whereas most women with oestrogen deficiency did not receive hormone replacement therapy.

**GH dose and IGF-I**

The mean ± s.d. dose of GH was 0.16 ± 0.08 mg/day (range 0.10–0.30 mg/day) and was numerically higher in women as compared with men (0.22 ± 0.08 vs 0.14 ± 0.07; P = 0.058). After treatment with GH for 6

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and 12 months, IGF-I levels were increased by GH, but not by placebo, compared with baseline (6 months, ΔIGF-I+88 ± 50 (GH) vs −17 ± 67 μg/l (placebo) and 12 months, ΔIGF-I+88 ± 72 (GH) vs −31 ± 47 μg/l (placebo); P<0.001). Women had lower IGF-I levels than men at baseline (116 ± 79 vs 182 ± 82 μg/l respectively; P=0.03); at the end of the study, IGF-I increased significantly by GH in both sexes, and to similar levels in men and women (185 ± 108 vs 229 ± 56 μg/l; P=0.50).

Cognition and mood

Table 2 shows the mean performance for each cognitive and mood measure in the placebo and GH groups during the study period. Of the 34 patients, 17 had been treated with radiotherapy for their pituitary tumours. These patients were evenly assigned to the GH and the placebo group respectively. We did not detect an effect of radiotherapy on the baseline cognitive function. At the 6-month assessment, there were improvements from baseline in the GH group for the digit learning test. The 12-month assessment, no significant benefits of GH were found. There were no significant changes of the mood measures during the study.

Safety parameters

Similar levels were seen in the GH and placebo groups: fasting glucose (4.9±0.7 vs 4.5±0.8 mmol/l), insulin (56±18 vs 50±22 pmol/l), and HbA1c (5.9±0.7 vs 5.8±0.5%) at baseline. After treatment, there were no significant differences between the GH and the placebo groups in terms of the changes from baseline for any of these parameters. The overall adverse event rates were similar in the GH and the placebo groups. One patient in the GH group died of an unrelated cause (acute bronchopneumonia) during the study. Another patient in the GH group was noted to have a suspected neoplasm on the left thigh on day 168 of treatment and was discontinued immediately. This was later

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<td>12.13 (6.19)</td>
<td>11.20 (5.39)</td>
<td>16.27 (5.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>11.56 (6.08)</td>
<td>10.88 (5.59)</td>
<td>13.67 (6.91)</td>
</tr>
<tr>
<td>Associate learning (recall)</td>
<td>Lower score = worse memory</td>
<td>GH</td>
<td>4.31 (2.12)</td>
<td>4.00 (2.14)</td>
<td>5.99 (1.81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>4.61 (2.20)</td>
<td>4.24 (2.11)</td>
<td>4.93 (2.46)</td>
</tr>
<tr>
<td>Continuous performance</td>
<td>Higher score = greater percentage of</td>
<td>GH</td>
<td>5.73 (6.50)</td>
<td>7.67 (8.18)</td>
<td>11.06 (9.14)</td>
</tr>
<tr>
<td></td>
<td>errors</td>
<td>Placebo</td>
<td>5.28 (6.08)</td>
<td>11.46 (9.83)</td>
<td>12.08 (11.48)</td>
</tr>
<tr>
<td>Symbol digit (incorrect)</td>
<td>Higher score = more errors</td>
<td>GH</td>
<td>2.88 (3.42)</td>
<td>2.53 (4.10)</td>
<td>1.73 (1.68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>3.22 (3.69)</td>
<td>2.59 (4.42)</td>
<td>1.87 (2.42)</td>
</tr>
<tr>
<td>Symbol digit latency</td>
<td>Higher score = responsive slowing</td>
<td>GH</td>
<td>170.14 (64.36)</td>
<td>170.99 (60.11)</td>
<td>161.17 (66.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>144.67 (34.04)</td>
<td>145.48 (34.60)</td>
<td>135.51 (32.14)</td>
</tr>
<tr>
<td>Pattern memory (correct)</td>
<td>Lower score = worse memory</td>
<td>GH</td>
<td>19.25 (2.59)</td>
<td>17.13 (5.68)</td>
<td>19.00 (3.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>19.72 (2.80)</td>
<td>18.24 (5.32)</td>
<td>18.33 (5.78)</td>
</tr>
<tr>
<td>Colour word correct</td>
<td>Lower scores = more incorrect</td>
<td>GH</td>
<td>42.17 (5.44)</td>
<td>41.50 (5.22)</td>
<td>42.56 (4.67)</td>
</tr>
<tr>
<td></td>
<td>responses</td>
<td>Placebo</td>
<td>42.53 (5.34)</td>
<td>42.13 (4.91)</td>
<td>40.77 (6.25)</td>
</tr>
<tr>
<td>Mood scores</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tension</td>
<td>Lower score = more tense</td>
<td>GH</td>
<td>8.13 (2.00)</td>
<td>9.00 (2.51)</td>
<td>10.09 (2.55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>10.44 (4.13)</td>
<td>10.24 (3.70)</td>
<td>9.93 (3.71)</td>
</tr>
<tr>
<td>Depression</td>
<td>Lower score = more depression</td>
<td>GH</td>
<td>7.25 (1.95)</td>
<td>7.27 (1.79)</td>
<td>8.36 (2.50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>8.61 (4.05)</td>
<td>9.18 (4.84)</td>
<td>8.73 (4.13)</td>
</tr>
<tr>
<td>Anger</td>
<td>Lower score = more anger</td>
<td>GH</td>
<td>6.25 (1.29)</td>
<td>6.53 (1.30)</td>
<td>7.91 (2.91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>8.17 (4.27)</td>
<td>7.65 (3.50)</td>
<td>7.60 (2.67)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Lower score = more fatigued</td>
<td>GH</td>
<td>14.00 (4.07)</td>
<td>14.47 (3.87)</td>
<td>15.55 (4.85)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>13.89 (4.76)</td>
<td>13.24 (5.41)</td>
<td>13.13 (4.82)</td>
</tr>
<tr>
<td>Confusion</td>
<td>Lower score = more confused</td>
<td>GH</td>
<td>8.63 (2.19)</td>
<td>9.27 (2.12)</td>
<td>10.64 (3.36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>10.50 (3.07)</td>
<td>9.35 (2.74)</td>
<td>9.87 (2.88)</td>
</tr>
</tbody>
</table>

Results are shown as mean (S.D.).

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diagnosed as a liposarcoma, the causality of which was undetermined. Two patients in the placebo group developed atrial fibrillation and non-sustained ventricular tachycardia during the study and subsequently underwent permanent pacemaker insertion. No clinically relevant effects were seen in either group in terms of vital signs, full blood count, renal or liver biochemistry (Fig. 2).

**Discussion**

This is the first controlled study of the effects of GH on cognition in elderly patients with GHD. The beneficial effects on cognition that occurred with GH therapy were discrete. Fewer subjects than anticipated were enrolled, which reflects the difficulty in identifying patients with sufficiently severe GHD at baseline that had not
previously received replacement therapy. This may have introduced a potential selection bias in favour of patients with minor cognitive deficits at baseline, and relatively little scope for improvement, since those with more marked symptoms are likely to have previously qualified for treatment. These aspects may have contributed to the relatively small effects observed.

In young adults with childhood-onset GHD, existing data argue for reduced memory and, possibly, reduced attention (20–22). In patients with adult-onset GHD, the data are less consistent; the presence/severity of cognitive deficits seems to be determined by underlying cause and its treatment (23–25). Subjects with large cognitive deficits seem to be determined by underlying data are less consistent; the presence/severity of cognitive deficits seems to be determined by underlying cause and its treatment (23–25). Subjects with large tumours, such as craniopharyngiomas requiring transfrontal surgery, have lower cognitive function than subjects requiring medical treatment only. However, suboptimal cognition has been found also in patients who had not been treated with surgery or radiotherapy (23), raising the possibility that hormonal abnormalities per se could be responsible. Another aspect for consideration is the duration of GHD, which is generally longer in patients with childhood-onset disease. The severity of GHD may also be more profound in young adults under the existing definition of GHD. However, elderly GHD patients also seem to have lower scores of psychological function as compared with their healthy peers reporting less energy and personal life fulfillment (3).

There are receptors for GH in many areas of the brain, including the hippocampus (26), a region associated with memory and learning processes. The binding sites for GH in the brain are particularly abundant in the choroid plexus (27). When administered subcutaneously, GH can cross the blood–brain barrier and influence cerebrospinal fluid concentrations of neurotransmitters, such as dopamine and aspartate (28). The importance of dopamine to attentional function is unequivocal (29), whereas aspartate is a ligand for the N-methyl-D-aspartate (NMDA) receptor that has been shown to have a role in the development of long-term memory in hippocampal cells (30). Subcutaneous injection of GH to rats induced an upregulation of the hippocampal GH receptor transcripts, which positively correlated to an increase in the NR2b gene transcript (31). Interestingly, overexpression of the NMDA receptor subunit NR2b in the forebrain of transgenic mice has been shown to enhance cognitive capabilities (32).

Relatively few clinical data on the effect of treatment with GH on cognition have been reported. Positive effects were observed in four open studies on a limited number of patients (14, 33–35). The study by Golgeli et al. used a neurophysiologic test, P300 event-related potential (ERP) latencies as detected by EEG, and found abnormally prolonged latencies in women with GHD as a consequence of Sheehan’s syndrome (33). Similar ERP findings have been reported in patients with Alzheimer’s disease (36) and in patients with depression (37). After 6 months of treatment with GH in women with GHD, ERP latencies were normalized, which the investigators interpreted as an improvement of the evaluation process (33). In addition to the open-label studies on GH and cognition, four placebo-controlled studies have addressed this topic (38–41). In two studies where deficits were present at baseline (38, 39), improvements of attention and memory were reported. On the other hand, GH did not enhance cognitive functions in patients with no known prior impairments (40, 41). The outcome was also dependent on the administered dose of GH and the duration of treatment, whereas age at onset of GHD did not seem to be a strong determinant, since positive and neutral effects were reported in both childhood- and adult-onset diseases.

Today, it is well recognized that men and women respond differently to GH treatment, with women requiring a higher dose of GH (42–45). The mechanism is not fully understood but has been attributed to circulating levels of oestrogens and in particular the hepatic concentrations of oestradiol (46), which possibly inhibit GH signaling by suppressing GH-induced JAK2 phosphorylation (47). Since a difference in dose requirements was also observed in these elderly patients in the absence of treatment with HRT in the women, it is unlikely that oestradiol concentrations is the only explanation for a gender difference in GH responsiveness, in particular as circulating oestradiol in the elderly is higher in the men (48). When treating elderly patients with GH, the different dose requirements should be considered in order to optimize treatment in all patients.

In the present study, benefits of GH treatment observed for the cognitive measures occurred because some aspects of cognitive function improved over the year in the GH therapy group while the placebo group deteriorated. The findings provide a basis for further studies with an emphasis on patients with severe cognitive impairment at baseline.

Acknowledgements

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