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Quality of life of growth hormone (GH) deficient young adults during discontinuation and restart of GH therapy

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Abstract

The present study evaluates the effects of one year of discontinuation and one year of growth hormone (GH) treatment on quality of life (QoL) in young adults with childhood-onset growth hormone deficiency (CO-GHD). Twenty-two subjects (14 males, 8 females; 11 isolated growth hormone deficient [IGHD], 11 multiple pituitary hormone deficient [MPHD]), aged between 15 and 22 years, on ongoing GH treatment were assessed during one year of discontinuation. Thereafter, 9 of these patients, who were found to be still GH deficient (GHD), added by 11 newly recruited GHD patients who also were not treated in the preceding year (in total 10 males and 10 females, aged between 17 and 27, 5 IGHD, 15 MPHD), restarted GH treatment for one year. During discontinuation and restart of GH treatment somatic and psychological assessments took place every 6 months. In the first 6 months of the GH discontinuation period insulin-like growth factor I (IGF-I) level significantly declined whereas no further decrease in IGF-I was seen after month 6. The number of psychological complaints and depression increased only during the first 6 months of discontinuation. Across the 12-month of discontinuation tension increased in MPHD and decreased in IGHD patients. Only in the first 6 months of GH treatment IGF-I level increased, anxiety decreased and QoL improved. Depression scores tended to decrease across the 12 month treatment period. During the 2-year discontinuation and treatment period intra-subject IGF-I level was negatively correlated with depression,

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fatigue, tension and anxiety and positively with vigor and memory. At the end of the treatment period all psychometric parameters were similar or even improved compared to those at the start of the discontinuation period. It is concluded that one year discontinuation of GH treatment leads to a decrease in QoL within 6 months which effect is counteracted within 6 months after restart of GH treatment.

Keywords: Growth hormone deficiency; Growth hormone replacement; Growth hormone discontinuation; Young adults; GHD; Mood; Memory

1. Introduction

Currently it is known that, besides having somatic effects, growth hormone (GH) also affects (neuro)psychological functioning. Adults with growth hormone deficiency (GHD) (not on treatment) feel less energetic, are emotionally more labile, and experience disturbances in sex life and feelings of social isolation at a significantly higher frequency than controls (Björk et al., 1989; McGauley et al., 1990; Mitchel et al., 1986; Rosén et al., 1994). The decreased psychological well-being may be related to GHD per se or may, in the case of multiple pituitary hormone deficiency (MPHD), be related with sub optimal replacement with levo-thyroxine, hydrocortisone or sex steroids. In one study, a reduced psychological well-being was only observed in MPHD patients, whereas cognitive impairments were detectable in both MPHD and isolated growth hormone deficient (IGHD) patients (Deijen et al., 1996). Psychological well-being may therefore be related to hormone deficiencies other than GHD, whereas the cognitive impairment results from GHD per se. A further support for a relationship between GHD and impaired cognitive functioning is given by studies on insulin-like growth factor I (IGF-I) plasma level and intellectual functioning. For instance, serum IGF-I concentration in GH-deficient males correlated positively with IQ score and education level (Deijen et al., 1996). More recently, IGF-I plasma levels of elderly healthy men and women were positively associated with Mini Mental State Examination (MMSE) scores (Rollero et al., 1998). Similarly, IGF-I levels in elderly healthy men were found to be associated with better performance in tests sensitive to the effects of aging (Aleman et al., 1999). Thus, the GH/IGF-I axis may play a role in the level of, in particular, cognitive functioning in healthy persons and GHD patients.

With respect to GH replacement, in the past fifteen years psychological effects have been observed mainly in patients with adult-onset GHD (AO-GHD) (Almqvist et al., 1986; Attanasio et al., 1997; Burman et al., 1995; Degerblad et al., 1990; Mårdh et al., 1994; McGauley et al., 1990; Whitehead et al., 1992). The impact of GHD and the effect of GH treatment on general well-being appears different for patients with AO-GHD and those with childhood-onset GHD (CO-GHD). Attanasio et al. (1997) demonstrated that CO-GHD adults scored better in quality of life assessments than AO-GHD patients, and observed that a treatment effect was detectable in AO-GHD, but not in CO-GHD adults. In contrast, with respect to neuropsychological

functioning, GH replacement has been found to improve memory function in adults with CO-GHD. Moreover, the changes in memory performance were positively correlated to the GH induced changes in serum IGF-I concentration (Deijen et al., 1998).

Although there is growing evidence of the psychological effects of GH treatment, the effects of discontinuation of GH treatment followed by a restart has not been studied yet. At present, discontinuation of GH therapy occurs once a child with GHD has reached final height. In healthy persons, GH secretion is known to continue, in lower dose, in adulthood. Discontinuation of GH therapy in GH deficient children may induce negative somatic and (neuro)psychological changes.

In the present study young GHD adults on ongoing GH treatment were followed for one year from the moment they discontinued GH therapy, after having reached final height. At different time points in this year we determined the effects of GH discontinuation on Quality of Life (QoL). In the second part of the study, the effects on QoL during one year of reinstitution of GH treatment were determined in those children who were GHD after this one-year discontinuation period, added with newly recruited CO-GHD patients not receiving GH during the past year.

We further questioned whether restart of GH therapy would cause QoL to return to the level seen at the end of the former GH therapy, immediately before the GH discontinuation period. In addition, we assessed the relationships between IGF-I serum levels and QoL parameters.

2. Materials and methods

2.1. Patients

2.1.1. GH discontinuation study

Twenty-two patients (14 males and 8 females), aged between 15 and 22 years (mean age 19 yr) were recruited from the outpatient clinic of the Vrije Universiteit Medical Center. They discontinued GH treatment after having achieved final height and closed epiphyseal plates. All patients were attending a secondary school. One female patient attended a special education school. They all were single. Patient characteristics are summarized in Tables 1 and 2. Eleven patients were diagnosed

Table 1
Patient characteristics (means±SD) in the discontinuation study

	Number of patients	Male	Female	Mean age	GHD	Non-GHD	Mean age diagnosis	Mean treatment duration	Mean SD difference from target height
IGHD	11	7	4	18.5±2.7	3	8	11±4	7.1±4.8	−1.1±0.83
MPHD	11	7	4	18.8±1.1	11	0	8.0±3.4	9.8±3.6	−0.12±1.1

Table 2
Diagnosis of the patients in the discontinuation study

Diagnosis	Number of patients
Tumor of the pituitary/craniopharyngeoma	2
Congenital malformation/anomaly	4
Perinatal trauma	6
Idiopathic	10

as being MPHD, 11 as IGHD. The diagnosis of GHD had been established during childhood. This was based on the presence of growth retardation, skeletal immaturity and a subnormal GH response. Since the group of patients consisted of late pubertal GH deficient young adults, the criteria for GHD were between the ranges for children and adults (a maximal GH response (following a GH stimulation test) in the past of $\leq$7 ng/ml (14 mU/l) (GHD) or $\geq$7 and $\leq$10 ng/ml (14–20 mU/l) (partial GHD). Following diagnosis, patients received GH replacement therapy for a duration of 8.4±4.4 years, including the year immediately prior to the start of the study.

At the beginning of the study patients were retested. Fourteen (64%) were still GHD and 8 (36%) were non-GHD, meeting the criteria for growth hormone deficiency in adulthood on two provocative tests (Arginine tolerance test and a GHRH-test (GHD$\leq$5 ng/ml (10 mU/l)).

Additional inclusion criteria were height increment less than 1 cm during the preceding 6 months, and normal thyroid, adrenal and gonadal function or stable hormonal replacement therapy with relevant hormones for at least 6 months.

2.1.2. GH treatment study

Nine patients (4 males, 5 females; 2 with IGHD and 7 with MPHD) who were diagnosed as GHD at the end of the discontinuation study took part in the GH treatment study. The mean age at the start of treatment was 21 yr, with a range between 18 and 27 yr.

Eleven patients were newly recruited from the outpatient clinic. These 11 patients were GHD since childhood and were not treated with GH during the past year.

Thus, this total group of 20 CO-GHD patients (10 males, 10 females; 5 IGHD and 15 MPHD) did not receive GH therapy during the preceding year. All patients were found to be still GHD at the start of GH treatment meeting the adult criteria on two provocative tests (Arginine tolerance test and a GHRH-test (GHD$\leq$5 ng/ml (10 mU/l)).

The mean age was 21 yr, with a range from 17 to 27 yr. All patients were single except 2 males who were in a steady relationship. Ten patients had a job. Three of these patients finished lower vocational education, 5 intermediate vocational education and 2 higher vocational education or university. Ten patients were still students; 2 were attending a school of lower vocational education, one a school of intermediate vocational education and 7 were attending a school of higher vocational

Table 3
Patient characteristics (means±SD) in the GH-treatment study

		Number of patients	Male	Female	Mean age	Mean age at diagnosis
Discontinuation and start	IGHD	2	1	1	24±3.5	5.5±2.1
	MPHD	7	3	4	21±1.5	9±3.7
Start study	IGHD	3	3	0	20.5±5	13±0
	MPHD	8	3	5	20±2.4	9.6±4.3
Total group		20	10	10	21±2.6	10±4.2

education or studying at the university. Patient characteristics are summarized in Tables 3 and 4.

2.1.3. Exclusion criteria and hormonal replacement

The exclusion criteria for all patients were diabetes mellitus, severe chronic diseases and diseases which may require corticosteroids in pharmacological doses, hypertension (BP consistently >160/95) active malignant disease or pregnancy or planned pregnancy during the study.

Conventional hormonal replacement therapy in the MPHD patients included testosterone undecanoaat, levo-thyroxine, hydrocortisone and vasopressin intranasal.

The study protocol was approved by the Medical Ethical Committee of the Free University Hospital, and all subjects gave their informed consent.

2.2. One year-discontinuation tests

To assess general well-being we selected questionnaires concerning fatigue, physical and psychological fitness and activity and concentration ability as suggested by McGauley et al. (1990). These questionnaires have documented sensitivity to measure the effects of drugs (van der Ploeg et al., 1980; Riezen and Segal, 1988; Wald and Mellenbergh, 1990).

Hopkins Symptom Checklist (HSCL). The HSCL (Derogatis et al., 1974) is a questionnaire which consists of three scales, i.e.: PSYCH-scale for the assessment of psychological complaints, SOMAT-scale for the assessment of somatic complaints

Table 4
Diagnosis of patients in the GH-treatment study

Diagnosis	Number of patients
Tumor of the pituitary/craniopharyngeoma	8
Congenital anomaly	6
Perinatal trauma	4
Idiopathic	2

and a TOTAL-scale including other psychoneurotic and somatic complaints such as anxiety and obsessive compulsive behavior, in addition to those of the PSYCH and SOMAT-scale. Responses are made by choosing from four response alternatives.

Profile of Mood States (POMS). The POMS (McNair et al., 1981; Shacham, 1983) is a questionnaire consisting of the subscales Depression, Anger, Fatigue, Vigor and Tension. All subscales except Anger were evaluated. The shortened Dutch version of 32 items was used (Wald and Mellenbergh, 1990). Responses are made by choosing from five response alternatives.

State–Trait Anxiety Inventory (STAI). The STAI (van der Ploeg et al., 1980; Spielberger, 1980) consists of a "state anxiety" and a "trait anxiety" scale. In the present study only state anxiety was assessed, which refers to situational anxiety. The subject is instructed to choose from four response alternatives.

2.3. Growth hormone re-treatment tests

During GH retreatment a Quality of Life scale was included that is not specific for GH deficiency. However, at the start of our study a QoL measure specific for GH deficiency was not available yet. In addition, we included a short- and long-term memory test. These tests have been found sensitive to measure the effects of drugs (Emmen et al., 1988; Deijen, 1993).

2.3.1. Profile of mood states (POMS)

State–trait anxiety inventory (STAI)

Symptom Checklist (SCL-90) (Derogatis and Cleary, 1977; Arrindell and Ettema, 1986). This checklist was used to replace the HSCL, because the SCL-90 covers a wider spectrum of psychopathology. The SCL-90 consists of the scales anxiety, agoraphobia, depression, somatic complaints, obsessive–compulsive behavior, interpersonal sensitivity, hostility, and insomnia.

Quality of Life scale (QLS) (Blau, 1977). The QLS is a positive scale evaluating how good people feel about relationships, eating and sleeping, and social achievements. It is a simple 10-item scale with response categories 'hardly satisfied' to 'very much satisfied'.

Short-term memory (STM): associate learning task (Emmen et al., 1988). Nine word pairs consisting of a name and an occupation are displayed on a computer screen at a constant rate of one pair per 3 s. After these pairs are presented, the subject is prompted nine times with one of the names and the nine occupation alternatives. Each time a name is presented, the subject has to choose one of the nine occupations by pressing the corresponding digit on the keyboard. After each answer the results are given in the following manner: "Yes, John is a grocer", or "No, Susan is a teacher". Three trials are given in which the subject has to learn as many paired names and occupations as possible. By means of this recognition procedure short-term verbal learning is measured.

Score: The number of correct associations on each trial (maximum score: 9).

Long-term memory (LTM): associate recognition task (Emmen et al., 1988). A single recognition trial of the nine names to be matched with one of the nine occu-

pations used in the associate learning test is administered at the end of the testing session. The approximate one-hour delay between this final testing and the associate learning task comprises a retention task for long-term memory.

Score: The number of correct responses (maximum score: 9).

2.4. Hormonal assays

Plasma GH (nmol/l) and IGF-I (mU/l) were measured with commercially available immunoradiometric assay; Sorin Biomedical, Sallugia, Italy and Webster, Texas, USA, respectively. After discontinuation of GH treatment, samples were obtained at week 0 and 1, and at months 3, 6, 9 and 12. After restart of GH therapy, samples were obtained at week 0 and at months 1, 2, 3, 6, 9 and 12. The samples were obtained in the morning after an overnight fast, when the patients visited the hospital. The age-related normal range of serum IGF-I for the participating group of males/females is 23–70 nmol/l.

2.5. Data analysis

Effects of discontinuation and restart of GH treatment during each 12-month period were assessed by means of one-way analysis of variance (ANOVA) with group (IGHD vs. MPHD; GHD vs. non-GHD) as independent factor and month as repeated measurements factor. ANOVAs were performed on the data from the one-year stop period and the one-year start period apart and on the data from the total 2-year stop and start period. The analyses of the stop and start study included 22 patients and those of the total 2-year period 9 patients.

Furthermore, to assess the relationships between IGF-I serum levels and psychological parameters Spearman correlations were computed within each patient between IGF-I serum concentration and mood/memory parameters at each time point. That is in each patient for the stop and start study IGF-I and mood/memory were correlated at 3 time points (months 0, 6 and 12) and at 6 time points for the total 2-year period. The calculated intra-patient correlations were averaged over patients leading to a mean intra-patient correlation between IGF-I and mood/memory at the different time points. The data are presented in Tables as mean±SD and shown in Figures as mean±SE. All calculations were performed with the Statistical Package for the Social Sciences, “SPSS/PC”.

3. Results

3.1. Discontinuation period

3.1.1. Changes in IGF-I and mood over 12 months in IGHD and MPHD patients

ANOVA with group as independent factor and month as repeated measurement factor revealed that the IGF-I level of the whole patient group including the later non-GHD patients meeting the adult criteria at that time, irrespective of IGHD/MPHD,

significantly declined over the year ($F(1, 20)=37.40$, $p<0.005$). The mean IGF-I values were 48, 19 and 20 at months 0, 6 and 12, respectively. There appeared to be a significant decline in IGF-I at month 6 compared to month 0 ($F(1,20)=78.71$, $p<0.005$). No difference in IGF-I was seen between month 6 and month 12. There was no significant difference between IGHD and MPHD in changes in IGF-I.

With respect to the HSCL a significant increase in psychological complaints (PSYCH scale) was found after 6 months of discontinuation ($F(1,20)=5.02$, $p=0.04$), but not across 12 months. Also, between month 6 and month 12 no difference in psychological complaints was found. No differences between MPHD and IGHD nor between GHD and non-GHD were found.

The depression scores (POMS) were significantly larger after 6 months ($F(1,20)=24.88$, $p<0.005$) and after 12 months ($F(1,20)=1.82$, $p<0.005$) of discontinuation. There was no difference between month 12 and month 6. There was a significant interaction between MPHD/IGHD and month, indicating an increase in depression in both groups until month 6 followed by a decrease in depression in MPHD and a continued increase in IGHD after 6 months ($F(1,20)=5.8$, $p=0.03$) (Fig. 1). With respect to tension (POMS) no significant main effect after 1 year was found. However, a significant interaction between group and month was found ($F(2,19)=5.17$, $p=0.02$). It appeared that between month 0 and 12 of discontinuation the tension in MPHD increased whereas the tension in IGHD patients decreased (Fig. 2).

With respect to the stop study depression scores (POMS) correlated negatively with IGF-I level, indicating that a lower level of IGF-I corresponds to less depression. The same was true for anxiety and psychological complaints. A positive relationship was found between IGF-I and vigor, indicating that a higher level of IGF-I is associated with more vigor (see Table 5).

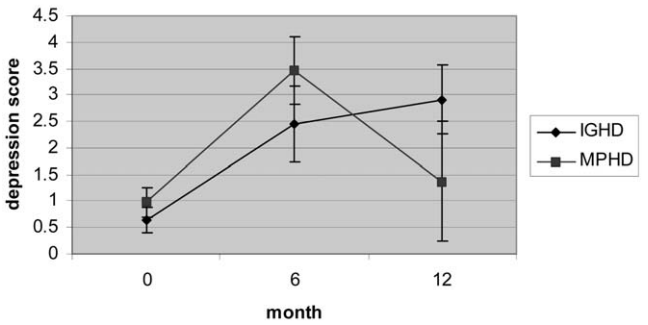

Fig. 1. Mean depression scores (POMS)±SE at months 0, 6 and 12 for the IGHD and MPHD patients in the discontinuation period.

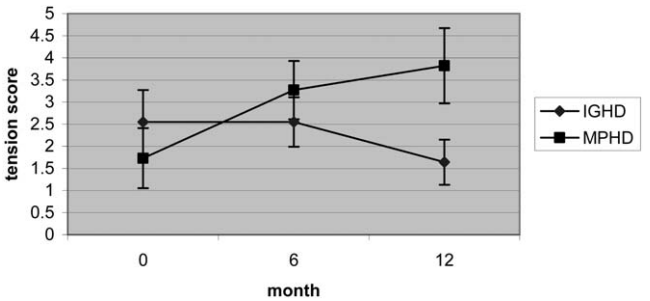

Fig. 2. Mean tension scores (POMS)±SE at months 0, 6 and 12 for the IGHD and MPHD patients in the discontinuation period.

Table 5
Mean intra-subject Pearson correlations between IGF-I level and mood parameters at months 0, 6 and 12 in the discontinuation study

	Depression (POMS)	Fatigue (POMS)	Vigor (POMS)	Tension (POMS)	Anxiety (STAI)	Psychological complaints (HSCL)	Somatic complaints (HSCL)
IGF-I	−0.42	−0.07	0.25	−0.22	−0.23	−0.35	−0.06

3.2. GH-treatment study

3.2.1. Changes in IGF-I, mood and memory over 12 months in IGHD and MPHD

ANOVA with group as independent factor and month as repeated measurement factor revealed that the IGF-I level of the whole patient group, irrespective of IGHD/MPHD, significantly increased over the year ($F(1,18)=27.66$, $p<0.005$). The mean values were 11, 33 and 38 at months 0, 6 and 12, respectively. There appeared to be a significant increase in IGF-I at month 6 compared to month 0 ($F(1,18)=50.75$, $p<0.005$. No difference in IGF-I level was seen between month 6 and month 12. There was no significant difference between IGHD and MPHD in changes in IGF-I.

Mood With respect to the SCL-subscale insecure there was a significant decline across the 12-month treatment period ($F(1,18)=4.71$, $p=0.02$). Post hoc tests indicated that this decrease was significant between month 6 and month 12 $F(1,18)=4.37$, $p=0.05$). This means that the decline in insecurity takes place in the last 6 months of the treatment period. No differences were found between IGHD and MPHD. Depression scores from the SCL tended to decrease across the 12-month treatment period ($F(1,18)=2.98$, $p=0.08$) (Fig. 3). Also, the anxiety scores (STAI) tended to decline across the 12-month period ($F(1,18)=2.80$, $p=0.09$). Post-hoc test revealed that a significant decline of anxiety only took place from baseline to month 6, indicating that anxiety decreases in the first 6-month treatment period ($F(1,18)=4.56$, $p=0.05$). There were no differences between IGHD and MPHD regarding the decrease in anxiety.

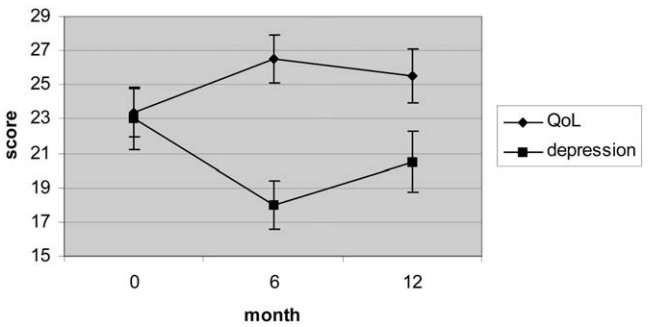

Fig. 3. Mean QoL and depression scores (POMS)±SE for all patients at months 0, 6 and 12 of the treatment period.

In line with the decrease in insecureness, depression and anxiety a significant improvement in QoL across the year was found ($F(1,18)=3.83$, $p=0.04$) (Fig. 3). This improvement was significant at month 6, indicating that QoL improves in the first 6-month treatment period ($F(1,18)=8.11$, $p=0.01$).

Memory Averaged over groups, short-term memory, assessed by the associate learning task, did not change in the course of the 12-month treatment period. However, there was a significant interaction between group (IGHD/MPHD) and month ($F(1,18)=3.72$, $p=0.05$ [trial 1] and $F(1,18)=6.27$, $p=0.025$ [trial 2], respectively). The memory scores of the patients tended to decrease in IGHD and to increase in MPHD from month 0 to month 6 ($F(1,18)=4.09$, $p=0.06$). After month 6 both groups showed an improvement (Fig. 4).

With respect to the treatment period negative correlations were found between IGF-I and depression, fatigue, tension and anxiety, whereas the correlations were positive for vigor, QoL and STM (see Table 6).

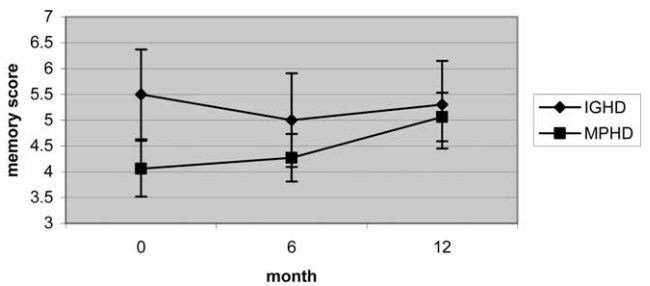

Fig. 4. Mean short-term memory scores (associate learning task)±SE for IGHD and MPHD patients at months 0, 6 and 12 of the treatment period.

Table 6
Mean intra-subject Pearson correlations between IGF-I level and mood/memory scores at months 0, 6 and 12 in the treatment study

	Depression (POMS; SCL)	Fatigue (POMS)	Vigor (POMS)	Tension (POMS)	Anxiety (STAI)	Quality of Life (QOLS)	Insecure (SCL)	STM
IGF-I	−0.32	−0.36	0.39	−0.312	−0.50	0.28	−0.18	0.20

3.3. Total 24-month stop/start period

A Manova with 6 repeated measurements (months 0, 6 and 12 of stop and start study) revealed a significant decline in anxiety (STAI) between months 0 and 6 of the start period ($F(1,8)=5.13$, $p=0.005$). The general pattern in anxiety is a nonsignificant increase in anxiety in the first 6-months of the stop period and a significant decline in anxiety in the first 6 months of the start study (Fig. 5). Depression (POMS) increased from month 0 to month 6 in the stop period and decreased from month 6 to month 12 ($F(1,8)=13.39$, $p<0.005$ and $F(1,8)=7.86$, $p=0.02$. There was no significant difference between month 0 in the stop period and month 12 in the start period. This means that after the treatment period depression returned to the same level as at the end of the former treatment.

With respect to fatigue (POMS) a significant decrease was found at the end of the treatment period compared to the start of the stop study ($F(1,8)=18.71$, $p<0.005$). A trend was found for a decrease in fatigue between months 6 and 12 of the treatment period ($F(1,8)=4.56$, $p=0.06$). In addition, vigor was increased at the end of the treatment period compared to month 0 of the stop study ($F(1,8)=5.27$, $p=0.005$). Finally, tension (POMS) tended to increase between month 0 and month 6 of the stop period ($F(1,8)=4.52$, $p=0.07$).

In the 2-year stop and start period in each subject correlations between IGF-I at months 0, 6 and 12 of the stop study and months 0, 6 and 12 of the start study

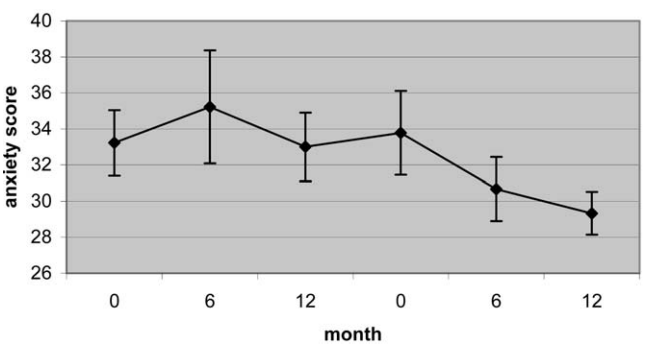

Fig. 5. Mean anxiety scores (STAI)±SE for all patients at months 0, 6 and 12 of the discontinuation period and months 0, 6, 12 of the treatment period.

indicated that higher IGF-I levels are associated with less depression, fatigue, tension, anxiety and with more vigor (see Table 7).

4. Discussion

During the 12-month discontinuation phase the IGF-I level declined, mainly in the first 6 months, equally in IGHD and MPHD patients. With respect to the QoL parameters, psychological complaints and depression increased in the first 6 months after discontinuation. Thus, the main changes in IGF-I concentration and mood parameters take place within 6 months. The negative intra-subject correlations of depression scores and psychological complaints with IGF-I plasma concentration indicate that the reduced mood is related to the decline in IGF-I level.

During discontinuation, tension increased only in MPHD. This is consistent with our former finding that patients with MPHD are more sensitive to stress than those with IGHD (Deijen et al., 1996). As a consequence, the psychological impact of stopping GH replacement increases tension particularly in MPHD patients. All patients were attending a school. As the patients did not report any drastic life events the observed psychological changes are not likely related with changes in life events.

In the GH treatment part of the study we clearly found an increase in IGF-I plasma concentration in the first 6 months of treatment in both IGHD and MPHD patients. In addition, in the first 6 treatment months anxiety was reduced and QoL improved. During the whole 12-month treatment period depression tended to decrease while insecureness decreased, most evident in the last 6 months of treatment. During treatment, we found that IGF-I concentration correlated negatively with anxiety, depression and tension and positively with vigor and QoL. However, memory was not improved during the treatment period. These findings indicate that GH treatment mainly improves QoL in the first 6 months of treatment, but more than 6 months are needed to improve mood. This is consistent with our earlier findings that in the first 6 months of GH replacement memory only improved in patients with a high IGF-I level. Patients with a normal serum IGF-I concentration required treatment for one year before memory improved (Deijen et al., 1998). During the GH treatment period some patients started a study at a school for higher vocational education or university. This can be considered an important life event which may partially account for the positive findings. However, the majority of the patients did not report

Table 7
Mean intra-subject Pearson correlations between IGF-I level and mood parameters at months 0, 6 and 12 in the discontinuation study and months 0, 6 and 12 in the treatment study

	Depression (POMS)	Fatigue (POMS)	Vigor (POMS)	Tension (POMS)	Anxiety (STAI)	Psychological complaints (HSCL)	Somatic complaints (HSCL)
IGF-I	−0.42	−0.07	0.25	−0.22	−0.23	−0.35	−0.06

any important changes in life events. In addition, we found substantial correlations between IGF-I concentration and psychological parameters. Therefore, the positive psychological effects can be attributed mainly to GH treatment.

With respect to the subjects who participated in the complete 2-year study period the same pattern as we described above emerged. During the first 6 months of discontinuation a deterioration of mood was seen which was reversed in the first 6 months of GH treatment. It is very important to note that there was no difference in depression and anxiety at the start of discontinuation and at the end of treatment. This means that GH replacement reverses the negative psychological effects of one year discontinuation of GH treatment.

We have previously shown that psychological well-being was reduced in MPHD, but not in IGHD patients (Deijen et al., 1996). In the present study we found that after discontinuation only tension increased in MPHD, suggesting that MPHD patients cannot handle the stress of GH discontinuation. It may well be true that the present sample sizes were too small to detect differences between IGHD and MPHD in other mood parameters. A remarkable result of the present study are the quite substantial intra-subject correlations between mood and IGF-I because of the few, i.e. three, observations within one subject. Considering the large interindividual differences in GH sensitivity (De Boer et al., 1996), the IGF-I response indeed seems a most valuable predictor of the impact of GH discontinuation or treatment on QoL.

It has been found that GH significantly affects neural cell metabolism in adult men in studies showing changes in cerebrospinal fluid concentration of the dopamine metabolite homovanillic acid following GH treatment (Burman et al., 1993; Burman et al., 1996; Johansson et al., 1995). The present study showed that mood impairment after GH discontinuation was counteracted by one year of GH retreatment. This strongly suggests that mood impairments in GHD subjects are related with a reversible GH-specific disturbance in neural cell metabolism.

References

Arrindell, W.A., Ettema, J.H.M., 1986. SCL-90. Handleiding bij een multidimensionele psychopathologie-indicator. Swets Test Services, Lisse.

Aleman, A., Verhaar, H.J.J., de Haan, E.H.F., de Vries, W.R., Samson, M.M., Drent, M.L., van der Veen, E.A., Koppeschaar, H.P.F., 1999. Insuline-like growth factor-I and cognitive function in healthy older men. Journal of Clinical Endocrinology and Metabolism 84, 471–475.

Almqvist, O., Thorén, M., Säfäf, M., Eriksson, O., 1986. Effects of growth hormone substitution on mental performance in adults with growth hormone deficiency: A pilot study. Psychoneuroendocrinology 11, 347–352.

Attanasio, A.F., Lamberts, S.W.J., Matranga, A.M.C., Birkett, M.A., Bates, P.C., Valk, N.K., Hilsted, J., Bengtsson, B.-Å., Strasburger,J., 1997. Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. Journal of Clinical Endocrinology and Metabolism 82, 82–88.

Björk, S., Jönsson, B., Westphal, O., Levin, J.-E., 1989. Quality of life of adults with growth hormone deficiency: A controlled study. Acta Paediatrica Scandinavica 356 (suppl.), 55–59.

Blau, T.H., 1977. Quality of life, social indicators, and criteria of change. Profess Psychol 8, 464–473.

Burman, P., Hetta, J., Karlsson, A., 1993. Effect of growth hormone on brain neurotransmitters. Lancet 342, 1492–1493.

Burman, P., Broman, J.E., Hetta, J., Wiklund, I., Erfurth, E.M., Hagg, E., Karlsson, F.A., 1995. Quality of life in adults with growth hormone (GH) deficiency: response to treatment with recombinant human GH in a placebo-controlled 21-month trial. Journal of Clinical Endocrinology and Metabolism 80, 3585–3590.

Burman, P., Hetta, J., Wide, L., Månsson, J.-E., Ekman, R., Karlsson, F.A., 1996. Growth hormone treatment affects brain neurotransmitters and thyroxine. Clinical Endocrinology 44, 319–324.

De Boer, H., Blok, G.J., Popp-Snijders, C., Stuurman, L., Baxter, R.C., van der Veen, E.A., 1996. Monitoring of growth hormone replacement therapy in adults, based on measurement of serum markers. Journal of Clinical Endocrinology and Metabolism 81, 1371–1377.

Degerblad, M., Almkvist, O., Grunditz, R., Hall, K., Kaijser, L., Knutsson, E., Ringertz, H., Thorén, M., 1990. Physical and psychological capabilities during substitution therapy with recombinant growth hormone in adults with growth hormone deficiency. Acta Endocrinologica 123, 185–193.

Derogatis, L.R., Lipman, R.S., Rickels, K., Uhlenhuth, E.H., Covi, L., 1974. The Hopkins Symptom Checklist. Pharmacopsychiatry 7, 79–110.

Derogatis, L.R., Cleary, P.A., 1977. Confirmation of the dimensional structure of the SCL-90: a study in construct validity. Journal of Clinical Psychology 33, 981–989.

Deijen, J.B., 1993. Vitamins and memory: niacin and vitamin B-6 in age-related cognitive decline. Ph.D.thesis, Free University, Amsterdam.

Deijen, J.B., de Boer, H., Blok, G.J., van der Veen, E.A., 1996. Cognitive impairments and mood disturbances in growth hormone deficient men. Psychoneuroendocrinology 21, 313–322.

Deijen, J.B., de Boer, H., van der Veen, E.A., 1998. Cognitive changes during growth hormone replacement in adult men. Psychoneuroendocrinology 23, 45–55.

Emmen, H.H., Hogendijk, E.M.G., Hooisma, J., Orlebeke, J.F. and Uijtdehaage, S.H., 1988. Adaptation of two standardized international testbatteries for use in The Netherlands for detection of exposure to neurotoxic compounds. Report, Medisch Biologische Laboratorium TNO, Rijswijk.

Johansson, J.-O., Larson, G., Andersson, M., Elmgren, A., Hynsjö, L., Lindahl, A., Lundberg, P.-A., Isaksson, O.G.P., Lindstedt, S., Bengtsson, B.-Å., 1995. Treatment of growth hormone-deficient adults with recombinant human growth hormone increases the concentration of growth hormone in the cerebrospinal fluid and affects neurotransmitters. Neuroendocrinology 61, 57–66.

Mårdh, G., Lundin, K., Borg, G., Jonsson, B., Lindeberg, A., 1994. Growth hormone replacement therapy in adult hypopituitary patients with growth hormone deficiency: combined data from 12 European placebo-controlled clinical trials. Endocrinology and Metabolism 1, 43–49.

McGauley, G.A., Cuneo, R.C., Salomon, F., Sönksen, P.H., 1990. Psychological well-being before and after growth hormone treatment in adults with growth hormone deficiency. Hormone Research 33, 52–54.

McNair, D.M., Lorr, M., Droppleman, L.F., 1981. Manual Profile of Mood States. Educational and Industrial Testing Service, San Diego, CA.

Mitchell, C.M., Joyce, S., Johanson, A.J., Libber, S., Plotnick, L., Migeon, C.J., Blizzard, R.M., 1986. A retrospective evaluation of psycho-logical impact of long-term growth hormone therapy. Clinical Pediatrics 25, 17–23.

van der Ploeg, H.M., Defares, P.B., Spielberger, C.D., 1980. Handleiding bij de Zelf-Beoordelings Vragenlijst ZBV. Een Nederlandstalige bewerking van de Spielberger State–Trait Anxiety Inventory. Swets and Zeitlinger, Lisse.

van Riezen, H., Segal, M., 1988. Comparative Evaluation of Rating Scales for Clinical Psychopharmacology. Elsevier, Oxford.

Rollero, A., Murialdo, G., Fonzi, S., Garrone, S., Gianelli, M.V., Gazzero, E., Barreca, A., Polleri, A., 1998. Relationship between cognitive function, growth hormone and insulin-like growth factor I plasma levels in aged subjects. Biological Psychiatry 38, 73–79.

Rosén, T., Johansson, G., Bengtsson, B.-Å., 1994. Consequences of growth hormone deficiency in adults, and effects of growth hormone replacement therapy. Acta Paediatrica 399 (suppl.), 21–24.

Shacham, S., 1983. A shortened version of the Profile of Mood States. J. Pers. Assess. 47, 305–306.

Spielberger, C.D., 1980. Test Manual for the State–Trait Anxiety Inventory—STAI form Y. Consulting Psychologists Press, Palo Alto, CA.

Wald, F.D.M., Mellenbergh, G.J., 1990. De verkorte versie van de nederlandse vertaling van de Profile of Mood States (POMS). Nederlands Tijdschrift voor de Psychologie 45, 86–90.

Whitehead, H.M., Boreham, C., McIlrath, E.M., Sheridan, B., Kennedy, L., Atkinson, A.B., Hadden, D.R., 1992. Growth hormone treatment of adults with growth hormone deficiency: results of a 13-month placebo controlled cross-over study. Clinical Endocrinology 36, 45–52.