Arq Neuropsiquiatr 1999;57(2-A): 182-189

IMPACT OF RECOMBINANT HUMAN GROWTH HORMONE (RH-GH) TREATMENT ON PSYCHIATRIC, NEUROPSYCHOLOGICAL AND CLINICAL PROFILES OF GH DEFICIENT ADULTS

A PLACEBO - CONTROLLED TRIAL

CLÁUDIO DE NOVAES SOARES[1,4], NINA ROSA MUSOLINO[1,2], MALEBRANCHE CUNHA NETO[1,2], MARIA ADELAIDE CAIRES[1,3], MARIA CRISTINA ROSENTHAL[1,3], CANDIDA PIRES CAMARGO[1,3], MARCELLO D. BRONSTEIN[1,2]

ABSTRACT - *Background:* Untreated GH-deficient adults have a diversity of dysfunctions (e.g. reduced muscle strength, emotional instability during stress, depressive symptoms) that may cause deleterious effects on quality of life, and may be positively influenced by recombinant human growth hormone (rh-GH) therapy. *Aim:* To evaluate the impact of a clinical intervention with rh-GH therapy on GH - deficient adults. *Method:* The physical, psychiatric and neuropsychological status of 9 GH-deficient adults was determined before and after the administration of rh-GH (0.250 IU/Kg/week) in a double blind placebo-controlled trial for six months. Patients then received rh-GH for a further period of 6 months and their status was re-evaluated. *Results:* Rh-GH was significant better than placebo at 6th month ($p<0.05$), producing increased serum Insulin like growth factor-I (IGF-1) levels, reduced body mass index (BMI) and body fat, increased lean body mass and water, reduced waist/hip ratio and increased energy expenditure. The rh-GH therapy was also significantly better than placebo on depressive features as measured by the Hamilton Depression Scale (17-items) ($p= 0.0431$) and the Beck Depression Inventory ($p= 0.0431$). Neuropsychological evaluations showed significant improvements in measures of Attention: Digit Backward ($p= 0.035$),Verbal Fluency (FAS) ($p= 0.02$) and Cognitive Efficiency (WAIS-R tests): Vocabulary ($p= 0.027$) , Picture Arrangements ($p= 0.017$), and Comprehension ($p= 0.01$) following rh-GH therapy. *Conclusion:* The clinical, psychiatric, and neuropsychological impairments of untreated GH-deficient adults can be decreased by rh-GH therapy.

KEY WORDS: growth-hormone deficiency, adult, treatment, psychiatry, depression.

Impacto do tratamento com hormônio de crescimento recombinante (rh-GH) sobre as características psiquiátricas, neuropsicológicas e clínicas de adultos com deficiência de GH: ensaio clínico duplo-cego controlado com placebo

RESUMO - *Introdução:* Pacientes com deficiência de hormônio de crescimento (GH) apresentam diversas alterações clínicas (ex: redução de massa muscular e de função cardíaca) e psíquicas (ex: quadros fóbicos, sintomas depressivos, déficits cognitivos). *Objetivo:* Avaliar o impacto da terapêutica com rh-GH em adultos com deficiência de GH. *Método:* Nove pacientes foram diagnosticados com deficiência de GH e então submetidos a ensaio clínico, duplo-cego, controlado, recebendo rh-GH (0,250UI/Kg/semana) ou placebo, por período de 6 meses. *Resultados:* Houve melhora significativa ($p<0,05$) em parâmetros clínicos (aumento de massa muscular, redução do índice de massa corpórea (BMI), aumento de gasto energético), psiquiátricos (sintomas depressivos avaliados pelas escalas de Beck e Hamilton ($p= 0,043$)) e neuropsicológicos (testes de atenção ($p= 0,035$), fluência verbal (FAS: $p= 0,02$), além da melhora de eficiência cognitiva (testes do WAIS-R: vocabulário ($p= 0,027$) , Arranjo de Figuras ($p= 0,017$), Compreensão ($p= 0,01$)). *Conclusão:* Prejuízos clínicos, psíquicos e neuropsicológicos causados pela deficiência de GH em adultos podem ser reduzidos pela terapêutica com rh-GH.

PALAVRAS-CHAVE: hormônio de crescimento, deficiência, adulto, tratamento, psiquiatria, depressão.

[1]Instituto de Psiquiatria, Hospital das Clinicas (HC), Faculty of Medicine of the University of Sao Paulo (FMUSP), Brazil; [2]Neuroendocrine Unit, Functional Neurosurgery Division, HC-FMUSP; [3]Division of Neuropsychology, Instituto de Psiquiatria, HC-FMUSP. [4]Department of Psychiatry, FMUSP. Aceite: 7-janeiro-1999.

Dr. Cláudio de Novaes Soares - Rua José Maria Lisboa 1060/21 - 01423-001 São Paulo SP - Brasil. Fax 55 11 2822501. e-mail: novaesc@ibm.net

Untreated GH-deficient adults have shown, due to their hormone deficiency, increased fat mass and reduced lean body mass, increased risk for cardiovascular mortality, myocardial function, and reduced muscle strength, as well as reduced exercise capacity, energy expenditure and basal metabolic rate. These conditions are commonly associated with reports of a "suboptimal well-being", including impaired psychological functions[1-3]. Correction of these abnormalities by GH replacement therapy were initially limited by the restricted supplies of GH. Unlimited production of GH was made possible by DNA technology[4]. Several studies explored the psychological difficulties among GH-deficient patients and the benefits after replacement therapy using quality-of-life questionnaires, particularly the Nottingham Healthy Profile (NHP) and the Psychological General Well-Being Index (PGWB)[5]. Although there are some reports of GH-deficient adults with normal achievements in the educational sphere, these individuals have higher rates of unemployment than the general population[1], less involvement in leisure activities, and show low levels of self-esteem, emotional instability during specific stress, a fatalistic attitude with a tendency towards depression, and a very strong feeling of being isolated from the outside world[6]. Recently, Nicholas et al.[7] compared GH-deficient (GHD)adults with non-GHD short adults and showed that some psychiatric disturbances among GHD, including high rates of social phobia cannot be explained by short stature alone. Furthermore, different research groups have reported that some abnormalities may improve during GH substitution, including the lean/fat body mass ratio and improvements in relation to intellectual potentialities[6].

Previous studies also leave doubts as to whether the reduced psychological well-being and neuropsychological performance among GH deficient patients are caused by GH deficiency *per se* or are related to other hormone deficiencies[8]. Deijen et al.[9] evaluated different groups, including men with multiple pituitary hormone deficiencies (MPHD) with severe impairment of GH, men with isolated growth hormone deficiency (IGHD) as well as healthy men as a control group. This study pointed out that , from a psychological point of view, MPHD and IGHD adult patients also behaved as distinct groups. MPHD patients had higher anxiety state scores, worse perceptual-motor skills and worse memory performance than controls. On the other hand, IGHD patients only showed subnormal memory performance. Despite all these considerations most of reports failed to identify previous neuropsychological and/or psychiatric features of these patients, towards better evaluate clinical effects of rh-GH replacement therapy.

This study aims to assess patterns of the present mental state and qualitative measures of clinical, psychiatric and neuropsychological improvements among GH-deficient adults submitted to rh-GH treatment trough more sensitive variables.

METHOD

Subjects

Patients attending the outpatient clinic of this Institute with GH deficiency diagnosed by insulin tolerance test [10] for at least two years, free of GH treatment during the last 12 months, and no acute severe illness during the last 6 months, chronic diseases (including liver or renal disease, diabetes mellitus, and hypertension),or history of malignancy (excluding cranial tumours or leukemia that might cause GH deficiency) were selected for this trial. After an informed consent had been obtained, the necessary diagnostic procedures were performed. Of the intend to treat sample of ten patients, one dropped-out at the beginning of the study, due to non-compliance. Nine patients (6 men) with GH deficiency (GHD), with a mean age of 39.4 years (range 28-52 yr) completed the study. Seven patients had acquired pituitary insufficiency in adult life due to sellar tumours. Some of them had their diagnosis (e.g. prolactinoma or craniopharyngioma) several years before this evaluation and had already been submitted to various therapeutic interventions (clinical, surgical or radiotherapy). Two patients had congenital GH deficiency. Table 1 characterises the clinical data of this sample.

Study design

A double-blind placebo-controlled trial with parallel groups, with patients randomly allocated in placebo group (n=4) or rh-GH (Genotropin®-Pharmacia) (n=5), self-administered sub-cutaneously through a pen (Kabipen®) daily for six months. The initial dose was 0.125 IU/Kg/week for the first month, and then increased to 0.250 IU/kg/week for the following 5 months. All patients were then treated for 6 additional months with rh-GH in an open phase of the trial.

Psychiatric evaluation

Following an open clinical interview, patients were assessed through the life-time version of the *Schedule for Affective Disorders and Schizophrenia* (SADS-L)[11]. Depressive symptoms were rated on the *Hamilton Depressive Scale* (HDS 17-item)[12]and *Beck Depression Inventory* (BDI)[13] at the beginning of the trial, at the end of the double blind placebo-controlled trial, and following the additional six months with rh-GH treatment (open phase of the trial).

Clinical assessment

The clinical evaluation included determinations of body mass index (BMI), waist/hip ratio (W/H), body composition by bioimpedance and dual energy x-ray absorptionmetry, and energy expenditure (EE) assessed by calorimetry.

Neuropsychological testing

Patients were submitted to a standardised neuropsychological evaluation[14] including a set of cognitive tasks and measurements of attention.

Measurements of attention- Digit Span Forward, a measurement of immediate memory recall; Digit Span Backward, a serial task of mental control; FAS test, measuring word fluency and self-monitoring capacity; Trail Making A ,a test of visual-conceptual and visual-motor tracking; Stroop Colour Test, a measurement of selective attention and response inhibition**.**

Cognitive tests- Vocabulary: for general ability through a word definition; Block Design: for non-verbal thinking and constructive abilities; Comprehension: for judgement or opinion on socially relevant topics; Picture Arrangement: measuring symbolic interpretation ability of social events ; Similarities : for verbal concept formation, and a estimated IQ (WAIS-R).

Statistical

The Wilcoxon's matched-pair signed rank test were used for between group and intra-group comparisons. The absolute values of the differences are calculated for each case and ranked from smallest to largest. The test statistic is based on the sums of ranks for negative and positive differences (SPSS 6.0 for Windows). Bonferroni corrections were used for guarding against an increase in the *Type I error* when performing multiple significant tests.

Table 1. Clinical and laboratorial data on patients.

Patients	Diagnostic	Treatment	Other Pituitary Hypofunctions	Maximum GH response to hypoglycemia (ng/ml)	GH deficiency diagnosis (years)
males					
1*	PA-NF	SURG + RT	TSH, ACTH, LH, FSH	0.5	8
2*	"empty sella"	-	LH, FSH	0.5	15
3*	PA - NF	SURG + RT	TSH, ACTH, LH, FSH	0.6	5
4*	PA - NF	SURG + RT	ACTH, LH, FSH	4.5	3
5*	PA - PRL	SURG + RT	LH, FSH	0.2	7
6*	idiopatic	—	TSH, LH, FSH	0.4	21
females					
7*	CRANIOP	SURG + RT	TSH, ACTH, LH, FSH	0.2	9
8*	PA - NF	SURG	—	2.4	7
9*	PA - PRL	SURG + RT	LH, FSH	1.0	9

ACTH, adrenocorticotropin; CRANIOP, craniopharyngioma; FSH, follicle-stimulating hormone; GH, growth - hormone; LH, luteinizing hormome; NF, non functioning; PA, pituitary adenoma; PRL, prolactinoma; SURG, surgery; RT, radiotherapy; TSH, thyroid-stimulating hormone.

RESULTS

Psychiatric evaluation

Six patients had previous depressive episodes as follows: puerperal depression (n=1), minor depressive episodes (n=1), major depressive episode (n=1), and post-surgical depressive episodes (n=3). One patient with no previous history of depression was depressed at intake in this trial but refused antidepressant treatment and insisted on trying rh-GH therapy instead. According to SADS-L criteria, three patients had unstable personality features, with some obsessive and phobic traits, those two who had congenital hypopituitarism and shorter statures.

Table 2 displays Beck Depression Inventory (BDI) and Hamilton Depressive Scale total mean scores. There were significant differences between the first Hamilton ‘s total mean scores (HDS) and the second evaluation following 6 months of rh-GH therapy ($p = 0.0431$), but not on placebo group ($p= 0.2733$). Similar results were found when Beck’s scores (BDI) were compared (rh-GH group: $p=0.0431$; placebo group: $p= 0.1088$).

Table 3 shows no differences between total mean scores of HDS ($p=0.1088$) or BDI ($p=0.0679$)after 6 and 12 months of rh-Gh treatment. Curiously, even the placebo group did not improve after 6 months of rh-Gh treatment, following the initial placebo response (HDS $p = 0.1088$; BDI: $p = 0.1441$)

Clinical assessment

There were no differences between initial and following 6 months measures of placebo initial users (n=4) and no differences between 6 and 12 months of rh-GH treatment group (n=5) Thus, the clinical and neuropsychological results were analysed comparing measures at the beginning of the study (baseline for rh-GH therapy group and after six months for placebo group), and following 6 months of rh-GH therapy of all patients.

Significant differences were pointed out ($p<0.05$) through an increase of serum IGF-1 levels, reduction in body mass index (BMI) and body fat, increase in lean body mass and water, reduction in waist/hip ratio (W/H), and increase in energy expenditure (EE).

Neuropsychological testing

Significant differences ($p<0.05$) were observed in Digit Span Backward, FAS test, Comprehension and Picture Arrangement.

Table 5 displays these values and the statistical analysis.

Table 2. Comparison of Hamilton Depression Scale (HDS) and Beck Depression Inventory (BDI) total mean scores between rh-GH and placebo groups before and after treatment (6 months).

Hamilton Depression Scale (total mean scores ± SD)			
	Pre -treatment	After 6 months of treatment	p values
Rh-GH group (n=5)	7.60 ± 5.81	2.20 ± 1.64	*0.0431
Placebo group (n=4)	4.75 ± 1.26	2.50 ± 2.64	0.2733
Difference between groups	NS (0.560)	NS (1.00)	
Beck Depression Inventory (total mean scores ± SD)			
	Pre -treatment	After 6 months of treatment	p values
Rh-GH group (n=5)	12.60 ± 7.02	4.20 ± 1.92	* 0.0431
Placebo group (n=4)	7.0 ± 3.16	4.50 ± 1.29	0.1088
Difference between groups	NS (0.138)	NS(0.71)	

Table 3. Comparison of Beck Depression Inventory (BDI) and Hamilton Depression Scale (HDS) total mean scores between 6 and 12 months of follow-up.

Hamilton Depression Scale (total mean scores ± SD)			
	After 6 months of treatment	After 6 additional months	p values
Rh-GH group (n=5)	2.20 ± 1.64	0.6 ± 0.54	0.1088
Placebo group (n=4)	2.5 ± 2.64	0.5 ± 1.0 (then receiving rh-GH)	0.1088
Difference between groups	NS (1.00)	NS (0.58)	
Beck Depression Inventory (total mean scores ± SD)			
	After 6 months of treatment	After 6 additional months	p values
Rh-GH group (n=5)	4.2 ± 1.92	1.80 ± 0.83	0.0679
Placebo group (n=4)	4.5 ± 1.29	1.75 ± 1.7 (then receiving rh-GH)	0.1441
Difference between groups	NS (0.71)	NS (0.80)	

Table 4. Clinical measurements of GH- deficient patients. Comparison of all patients' measurements initially and following 6 months of rh-GH therapy (n=9).

Parameters	Basic measurements (means)	After 6 months of rh-GH therapy (means)	z	p values
Body mass index BMI (Kg/m3)	26.5	25.9	2.19	0.028
Body fat (Dexa) (g)	23869.6	19766.4	2.66	0.007
Lean body mass (Dexa) (g)	42945.2	45546.8	1.95	0.05
Energy expenditure	1325.5	1488.9	2.43	0.015
Lean body mass (BIA)	48.3	50.4	2.07	0.038
Body fat (BIA)	21.2	17.6	2.66	0.007
Waist/hip ratio	0.97	0.95	2.19	0.028
TBW (BIA)	35.9	37.2	2.31	0.021
IGF - 1 (ng/ml)	29.3	267.6	2.72	0.008

BMI, Body Mass Index; LBM, Lean Body Mass; IGF-1, Insulin-like growth factor - 1.

Tabela 5. Significant findings of neuropsychological testings of GH - deficient patients. Comparison of all patients' measurements initially and following 6 months of rh-GH therapy (n=9).

Testings	Basic measurements (Means)	After 6 months of rh -GH therapy (means)	z	p value
Picture arrangement	9.5	11.9	- 2.52	0.011
Vocabulary	10.5	11.5	2.20	0.027
Comprehension	10.1	12.6	-2.37	0.010
FAS (Verbal fluency)	36.9	40.9	2.66	0.007

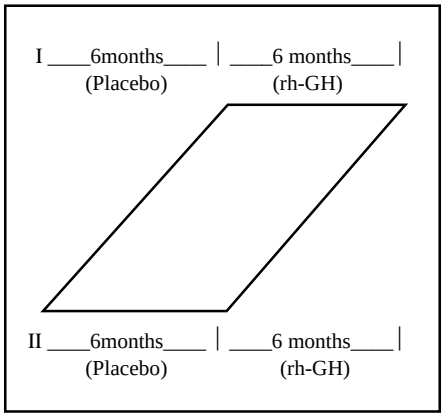

Fig 1. Clinical and neuropsychological improvements with rh-GH treatment: Study Design (n=9).
Note: Clinical and neuropsychological changes were analysed comparing the data collected initially from all patients (at the baseline of the treatment for the rh-GH group and after 6 months of placebo for the placebo group) with the data collected after 6 months of rh-GH therapy for all patients (after the 6 months of rh-GH therapy on placebo group and after the first 6 months of treatment on rh-GH group).

DISCUSSION

Regarding the observed clinical changes during rh-GH therapy, these improvements strengthened previous studies showing body transformations after rh-GH therapy, which could be related to the increase of physical "well-being" described after treatment [15] . Beneficial effects of this treatment ,as seen in this present study, strongly suggests clinical reasons to the introduction of this treatment as a routine procedure for GH deficient patients, as previously showed by the literature[16,17].

There are, however, some controversial aspects of the potential psychological effects of GH therapy. Scarce data about psychiatric morbidity among GH deficient adults focused phobic states. The prevalence of social phobia seems to be very high among GH deficient adults rising up to 35% of the sample group studied by Stabler et al.[18] compared to 10% among normal controls with short stature. There are also some reports of decreased self-esteem that could reflect depressive states[18]. Despite this, it is not clear if these patients have a *depressive* or a *apathetic* state due to GH deficiency as they reported feelings of isolation, less desire to interact with people, and less initiative for work and social activities. McGauley et al.[19] showed significant psychological improvements in energy level and mood in a double-blind, placebo-controlled six-months trial, administering rh-GH (0.07IU/kg body weight/day). Psychological well-being, however, remained unchanged in a study by Whitehead et al[20].

The clinical interviews and the scores in BDI and HDS of the sample studied showed that most of these patients did not have a present depressive episode, but depressive and apathetic features. Psychiatric evaluations showed improvements among patients following rh-GH therapy, as shown by their scores of BDI and HDS, their reports of "well-being" and their increased desire to social interaction reported.

It should be considered if the amelioration of "quality of life" and "psychological well-being" reported should be attributed to a direct effect of GH therapy on mood or to the combination of physical, psychological and cognitive improvements due to the correction of this hormone deficiency.

The neuropsychological findings of these data signalled significant changes in the most sensitive measurements of attention and motivational components. It is also worthwhile emphasise that the sample studied might be considered as an isolated GH-deficiency group for they had already been previously submitted to appropriate replacement of the other hormones for a period of at least 6 months. Thus, it was possible to attribute both cognitive and psychological improvements exclusively to rh-GH therapy.

The mechanisms underlying the beneficial results of rh-GH therapy on psychological well-being are still unclear. There is a possibility that the normalisation of body composition and the subsequent improvement in exercise capacity and physical well-being may contribute to the psychological improvement observed[16].

Nevertheless, a direct neuro-endocrine effect on the central nervous system (CNS) should be considered. The effects of GH on the CNS have been previously discussed[21,22]. GH receptors have

been found in some locations in the brain (e.g. the hippocampus and the hypothalamus)[23]. However, the physiological importance of these GH binding sites is unascertained. Johansson et al[21] showed in a double-blind placebo-controlled study that rh-GH treatment causes a ten-fold GH increase in the CSF, suggesting that rh-GH does pass the human blood-CSF barrier. The concentration of GH in the cerebrospinal fluid (CSF) is still low compared with serum (about 5%). In another study, patients after rh-GH treatment showed a lower concentration of homovanillic acid (HVA) in the CSF compared to controls, indicating a changed dopamine metabolism[24]. Higher CSF concentrations of excitatory amino acid aspartate in the group treated with rh-GH indicated that the decrease of HVA could be mediated by N-methyl-D-aspartate receptor, involving in dopamine release. These observation (decrease of HVA in the CSF) may be compared to similar changes found among patients after successful treatment of depressive episodes with antidepressant drugs[25] and may reflect a mechanism of action and a potential effect of rh-GH therapy on mood and behaviour[26].

The safety of GH treatment is an important point to be considered. There are still some discussion about the increased risk of tumour relapse or progression with GH therapy. Ogilvy-Stuart[27] studied 368 children treated for brain tumours or acute lymphoblastic leukaemia. Rates of tumour relapse were not greater in 62 children receiving GH replacement therapy for radiation-induced GH deficiency, even in children who had been reported as showing residual tumour after initial treatment, compared with 306 children not receiving GH therapy.

Rh-GH therapy may play an important role in the quality of life of GH deficient adults, through an improvement in physical conditions as well as directly on mood and cognition. There is, however, a lack of long-term follow ups of the beneficial effects of rh-GH therapy on psychiatric conditions.

REFERENCES

1. Dean HJ, Mc Taggart TL, Fish DG, et al. The educational vocational and marital status of growth hormone-deficient adults treated with growth hormone during childhood . Am J Dis Child, 1985,139:1105-1110.
2. Jorgensen JOL, Muller J, Moller J, et al. Adult growth hormone deficiency. Horm Res 1984,42:235-241.
3. Burman P, Broman E, Hetta J, et al. Quality of life in adults with growth hormone (GH) deficiency; response to treatment with recombinat human GH in placebo-controlled month trial. J Clin Endocrinol Metab 1995,80:3585-3590.
4. Björk S, Jönsson B, Westphal O, Levin JE. Quality of life of adults with growth hormone deficiency: a controlled study. Acta Paediatr Scand 1989;Suppl:356:55-59.
5. McGauley GA. Quality of life assessment before and after growth hormone treatment in adults with growth hormone deficiency. Acta Paediatr Scand 1989;Suppl:356:70-72.
6. Sartorio A, Molinari E, Riva G, Conti A, Morabito F, Faglia G. Growth hormone treatment in adults with childhood onset growth hormone deficiency: effects on psychological capabilities. Horm Res 1995;44:6-11.
7. Nicholas LM, Tancer ME, Silva SG, Underwood LE, Stabler B. Short stature, growth hormone deficiency, and social anxiety. Psychosom Med 1997;59:372-375.
8. De Boer H, Blok GJ, van der Veen EA. Clinical aspects of growth hormone deficiency in adults. Endocr Rev 1995;16:63-86.
9. Deijen JB, de Boer H, Bok GJ, van der Veen EA. Cognitive impairments and mood disturbances in growth hormone deficient men. Psychoneuroendocrinology 1996;21:313-322.
10. Hoffman DM, O'Sullivan AJ, Baxter RC, Hokky C. Diagnosis of growth hormone deficiency in adults. Lancet 1994;343:1064-1068.
11. Endicott J, Spitzer RL. A diagnostic review: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978;35:837-844.
12. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278-296.
13. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry, 1961;4:561-582.
14. Lezak MD. Neuropsychological assessment, 3Ed, New York: Oxford Univ Press, 1995.
15. Salomon F, Cuneo RC, Hesp R, Sönksen PH. The effects of treatment with recombinant human growth hormone in body composition and metabolism in adults with growth hormone deficiency. N Engl J Med,1989;321:1797-1803.
16. Johannson G, Rosén T, Lindstedt G, Bosaeus I, Bengtsson BA. Effect of two years of growth hormone treatment on body composition and cardiovascular risk factors in adults with growth hormone deficiency. Endocrinol Metab,1996;3:3-12.
17. Deijen JB, van der Veen EA. Growth hormone replacement and psychological changes in adults with growth hormone deficiency. Endocrinol Metab 1996;3:25-30.
18. Stabler B, Tancer ME, Ranc J, Underwood LE. Evidence for social phobia and other psychiatric disorders in adults were growth deficient during childhood. Anxiety, 1996;2:86-89.
19. McGauley GA, Cuneo RC, Salomon F, Sönksen PH. Psychological well being before and after growth hormone treatment in adults with growth hormone deficiency. Horm Res 1990;33:52-54.

20. Whitehead HM, Boreham C, Mcllrath EM, et al. Growth hormone treatment of adults with growth hormone deficiency:results of a 13-month placebo controlled cross-over study. Clin Endocrinol 1990;36:45-52.
21. Johannson JO, Larson G, Andersson M, et al. A Treatment of growth hormone (GH) - deficient adults with recombinant human GH increases the concentration of GH in the cerebrospinal fluid and affects neurotransmitters. Neuroendocrinology 1995;61:57-66.
22. Nyberg F, Burman P. Growth hormone and its receptors in the central nervous system- location and functional significance. Horm Res 1996;45:18-22.
23. Lai Z, Emtner M, Roos P, Nyberg F. Characterisation of putative growth hormone receptors in human choroid plexus. Brain Res 1991;546:222-226.
24. Burman P, Hetta J, Karlsson A. Effect of growth hormone on brain neurotransmitters. Lancet 1993;342:1492-1493.
25. Risby ED, Hsiao JK, Sunderland T, Agren H, Rudorfer MV, Pottter WZ. The effects of antidepressants on the cerebrospinal fluid homovanilic acid /5-hidroxyindolacetic acid ratio. Clin Pharmacol Ther 1987;42:547-554.
26. Wide L, Mansson JE, Ekman R, Karlsson FA. Growth hormone treatment affects brain neurotransmitters and thyroxine. Clin Endocrinol 1996;44:319-324.
27. Ogilvy-Stuart A Association between GH therapy and tumour relapse. Presented at 31st Annual Meeting of the European Society for Paediatric Endocrinology (ESPE). Zaragoza, Spain: September 1992.