CLINICAL STUDY

Growth hormone deficiency in pituitary disease: relationship to depression, apathy and somatic complaints

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Abstract

Objective: Adults with GH deficiency (GHD) have been reported to suffer from increased levels of depression and apathy, which are thought to contribute to the reduced quality of life observed in these patients when compared with healthy controls. Recent studies, however, cast doubt on the attribution of these impairments to GHD as opposed to an unspecific stress response to the chronic medical condition.

Design: To further clarify this relationship, we used psychometric tests to quantify depression, apathy and typical psychosomatic complaints in patients with different types of pituitary disease and compared the results with measurements of the patients' widely varying GH status.

Subjects and methods: In 98 patients, serum IGF-I was measured and at least one provocative test of the somatotrope pituitary axis was performed (GH-releasing hormone test (GHRHT) and/or insulin tolerance test (ITT)). All patients completed a set of well-established psychometric instruments (Beck Depression Inventory (BDI), Apathy Evaluation Scale (AS) and List of Somatic Complaints (LSC)). In addition, AS was administered in an informant report version for completion by a close relative or friend to verify the validity of the patient's self assessment.

Results: No relationship between measures of GHD (IGF-I, GHRHT and ITT) and psychometrically measured depression, apathy or psychosomatic well-being was found. A highly significant linear correlation between scores of all psychometric instruments (BDI, AS and LSC) was found.

Conclusions: The absence of any relationship between the severity of GHD and the level of depression/apathy/psychosomatic complaints suggests that these impairments are not specific symptoms of GHD. The reported improvement of these symptoms under GH substitution therapy might thus be interpreted as a secondary effect of somatic effects of GH substitution. Consequently, indication for GH substitution therapy should not be based on psychological impairments alone without the presence of somatic symptoms of GHD.

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Introduction

A large number of studies have contributed to the emerging definition of a growth hormone deficiency (GHD)-specific syndrome based on biological parameters, such as cardiovascular risk factors and bone composition. However, the impairment of psychological parameters in adults with GHD, such as memory performance and mood, which contribute to quality of life (QoL) as the parameter most commonly described to be impaired in GHD, remains a major justification for substitution therapy. In some studies, depression is one of the symptoms reportedly found in adults with GHD (1), while other reports find no significant difference between adults with GHD and controls as far as depression is concerned (2). In some studies, GH replacement is reported to have a beneficial effect on depression (3), while others observe no significant

improvement of depressive symptoms (4). In most cases, standardised self-report questionnaires are used to assess the degree of depression present in the subjects, making a quantification of this suspected symptom possible. Validity of the psychometric results obtained may be affected by a possible lack of insight reported in subgroups of patients treated for pituitary adenoma (5). In an attempt to improve the monitoring of GHD-related QoL impairment, particularly during substitution therapy, the QoL Assessment in GHD Adults (QoL-AGHDA) has been developed (6). This specifically designed instrument was recently shown to be unable to discriminate between patients with GHD and active acromegaly (7), casting further doubt on the attribution of impaired QoL to GHD.

The currently accepted standard diagnostic procedure for GHD in adults is the insulin tolerance test (ITT) (8). In patients with contraindications to the

ITT, alternative provocative tests of GH secretion must be used, all with less established diagnostic values than the ITT. One commonly employed test is the GH-releasing hormone test (GHRHT). Insulin-like growth factor-I (IGF-I), as a biochemical marker of GH action, may be useful for screening purposes and is the currently recommended parameter for monitoring GH substitution (8), despite its sensitivity to various influences independent of GH status (9).

All methods commonly used in the diagnosis of GHD yield quantitative results which are supposed to reflect the severity of GHD present. The self-report questionnaires for depression that are usually applied aim at quantifying this possible symptom. However, to the best of our knowledge, the quantitative analysis of a possible relationship between the degree of GHD and the severity of depression as expressed in quantitative parameters has not proceeded so far. This quantifying approach could, however, help to differentiate a specific, possibly biological, risk for depression in GHD, which would help to justify substitution treatment, from an unspecific risk for reactive depression as a consequence of the stress response to the circumstances associated with GHD as a chronic health condition.

We therefore measured depression, together with apathy and psychosomatic well-being as related psychological parameters all contributing to the QoL construct, using well-established psychometric scales. The scores thus obtained were then compared with the inter-individually varying degree of GHD, represented by IGF-I, ITT and GHRHT values, in 98 patients with pituitary disease and GH status ranging from elevated to severely deficient to evaluate a possible relationship.

Subjects and methods

Patients

All 240 patients with pituitary disease who had undergone endocrinological examination at our unit in 1999 were asked to complete a set of self-report questionnaires; 142 complied with our request. Of these, for the purposes of this report, only those who had been subjected to provocative testing of the somatotrope axis (ITT or GHRHT or both) and measurement of IGF-I serum concentration in the course of routine examination were considered ($n = 98$). All patients were on adequate and stable substitution treatment for pituitary deficiencies other than GH and none received GH replacement therapy (for further characteristics see Table 1). Of those with a history of hormonal hypersecretion, all but two patients with GH-secreting adenomas and seven with prolactinomas were cured at the time of examination.

GH status

Serum GH was measured using the 'CoatRIA' immunoradiometric assay from BioMérieux, Lyon, France. Results are given in ng/ml. IGF-I was assessed using the IGF-I 100T kit from Nichols Institute Diagnostics, San Juan Capistrano, CA, USA.

GHRHT was performed in the course of a combined releasing hormone test using GHRH (Ferring GmbH, Kiel, Germany). GH was measured 0, 15, 30 and 60 min after intravenous injection.

ITT was performed by measuring blood glucose and serum GH concentrations after i.v. injection of 1.2 IU/kg body weight insulin (Insulin Actrapid HM;

Table 1 Patients' characteristics.

	Males	Females	Total
Age (years)*	59.4±2.1	53.0±1.8	55.9±1.4
Duration of pituitary disease (years)*	4.93±0.69	7.93±1.2	6.58±0.74
Diagnosis			
Inactive pituitary adenoma	22	15	37
Prolactinoma	8	15	23
GH-secreting adenoma	5	16	21
Cyst	4	3	7
Other	5	5	10
Treatment			
Conservative	9	18	27
Transsphenoidal surgery	30	30	60
Repeated surgery†	5	6	11
Radiation therapy	0	2	2
Number of pituitary deficits other than GH			
None	17	29	46
One	10	14	24
Two	6	8	14
Three	6	3	9
Four	5	0	5

* Values are mean±S.E.M.

† Transsphenoidal and/or transfrontal.

Novo Nordisk Pharma, Mainz, Germany) at 0, 15, 30 and 60 min. Sufficient hypoglycaemia was considered to be achieved with blood glucose levels below 40 mg/dl and less than 50% of the initial value. For both types of provocative tests, peak GH concentration and the total area under the GH curve (AUC-GH) were determined.

Psychometric instruments

Three types of well-established self-report questionnaires were administered. Evaluation of all questionnaires used produces numerical scores with higher values indicating higher levels of depression, apathy and somatic complaints respectively.

Beck Depression Inventory (BDI) The German version (10) of the widely used 21-item self-report instrument designed to assess the severity of depression in adults and adolescents (11) was used. Each of the items is concerned with one aspect of the experience and symptomatology of depression (e.g. mood, libido) and consists of four statements with graded severity.

Apathy Evaluation Scale (AS) The German translation of the 18-item apathy scale (12) was applied in the self-report version (AS-S) and the informant report version (AS-I) which was to be completed by a close relative or friend of the patient.

List of Somatic Complaints (LSC) The German 'Beschwerden-Liste' is a standardised clinical instrument for the assessment of physical complaints related to subjective well-being (13). Both versions of 24 items each were applied (LSC and LSC').

Statistical analysis

Descriptive results are presented as median (range) when data did not fit normal distribution except when comparison with external results, which use mean and standard deviation as descriptive measures, is intended. For group comparisons, the Mann-Whitney U test was used; this does not require data to be normally distributed and is stable against outliers. Significances are two-tailed. To estimate the power of negative U-test results of group comparisons of BDI test results, a Monte Carlo simulation model was employed. Alternative 'sick' distributions with increasing median BDI scores were generated by stochastically mixing the found empirical distribution with a pre-treatment distribution of BDI scores of a population of depressive patients from Hautzinger *et al.* (14), whose post-treatment distribution of BDI scores was close to that of our patients. For each discrete mixing ratio, $n = 1000$ simulations were run. The probability of detecting the group difference on a two-tailed significance level of 0.05 was determined. Average medians of

'sick' distributions for power levels of 80% and 90% are given.

Correlations were sought by calculating Pearson's linear correlation coefficient (r) when linear dependency was graphically evident, otherwise Spearman's non-parametric correlation coefficient (ρ) was calculated; this does not require normal distribution and is stable against outliers. In correlation/regression analysis, IGF-I levels below the detection limit of the assay used (32 ng/ml) were given a value of 0 ng/ml. AUC-GH for ITT and GHRHT was calculated by trapezoidal integration. GH levels below the detection limit (0.3 ng/ml) were assumed to be zero for this purpose. All calculations were done using SPSS for Windows Release 10.0.7.

Results

Measures of GHD

While IGF-I was measured in all patients ($n = 98$), GHRHT was performed in 59, ITT in 32 and both provocative tests in seven cases. Non-parametric correlation between IGF-I and peak – as well as AUC-GH in ITT – was highly significant with $\rho = 0.59$, $P < 0.001$ and $\rho = 0.6$, $P < 0.001$ respectively, while non-parametric correlation between IGF-I and peak – as well as AUC-GH in GHRHT – was less significant with $\rho = 0.3$, $P < 0.05$ for both parameters. The distribution of all parameters of GH status was continuous except for outliers but not normal. Using a cut-off value of 3 ng/ml for peak GH, 41 patients (41.8%) showed insufficient response in one of the stimulation tests. IGF-I was subnormal in 34.7% of the patients (normal range 123–463 ng/ml for this age group). No significant gender difference was observed in IGF-I or ITT, while females had significantly higher GHRHT values (Table 2).

Questionnaires

Questionnaire score distribution was similar to that of reference populations and did not show significant gender differences (Table 3). A highly significant linear correlation between scores of all psychometric instruments was found (BDI, AS and LSC). In particular, AS-S and AS-I correlated linearly with $r = 0.69$, $P < 0.0001$.

To assess the quality of the patients' self assessment, the absolute values of the difference between AS-S and AS-I were calculated. Differences between groups which had received no surgical treatment, transphenoidal surgery and repeated surgery failed to reach significance, although those who had been subjected to surgery more than once ($n = 10$) showed higher mean deviation of self report and informant report scores (4.2 ± 0.83 , 4.1 ± 0.45 and 6.1 ± 1.8).

Table 2 Measures of GH deficiency: IGF-I, ITT and GHRHT. Values are median (range). Number of cases is shown in square parentheses.

	Males	Females	P
IGF-I (ng/ml)	135 (32–556); [44]	152 (32–707); [54]	0.300
ITT			
Peak GH (ng/ml)	2.55 (0–24.5); [16]	5.80 (0–39.4) [23]	0.135
AUC-GH (ng min/ml)	147 (0–970); [16]	309 (0–2750); [23]	0.376
GHRHT			
Peak GH (ng/ml)	2.8 (0–19.2); [31]	4.7 (0.4–39.8); [35]	0.02
AUC-GH (ng min/ml)	140 (0–786); [31]	192 (17.3–2740); [35]	0.011

Relationship between measurements of GHD and BDI, AS and LSC scores

No relationship between questionnaire scores (BDI, LSC, AS) and measurements of GHD (IGF-I, AUC-GH and peak GH in ITT and GHRHT) was observed (e.g. IGF-I vs BDI: Fig. 1), with correlations failing to reach significance in the whole group as well as for men and women separately, except between AS-I and AUC-GH in ITT in women, which both, unlike the other parameters, correlated independently with age. To exclude a possible effect of covariation, a correction for age, using linear regression, was performed. Afterwards, correlation was well beneath the level of significance ($\rho = 0.10$).

Patients with subnormal IGF-I values did not differ significantly from those with higher IGF-I values with respect to psychometric results (median and range in parentheses). The values for BDI are: 7 (0–20) $n = 34$ and 6 (0–34) $n = 64$; $P > 0.9$ in U test, detectable average median of deficient group at 80.6% power: 11.6, at 90.5% power: 13.0. No significant difference was found between patients with insufficient and normal response in stimulation tests. The values for BDI are: 6 (0–34) $n = 41$ and 6 (0–29) $n = 57$; $P > 0.85$ in U test, detectable average median of deficient group at 83.9% power: 11.1, at 90.2% power: 12.2. Psychometric results did not depend on the patients' number of pituitary deficiencies other than GH (patients with more than two deficiencies are represented by solid symbols in Fig. 1; BDI results grouped

by number of pituitary deficiencies other than GH are shown in Fig. 2; other data not shown).

Comparison of patients with low depression scores with patients who scored higher in the BDI, using an arbitrary BDI score of 6 (=median of the whole group) as cut-off value, did not reveal significant differences as far as IGF-I levels, ITT results and GHRHT results were concerned. Similar observations were made when using AS or LSC results as subdivision criteria.

Discussion

Study set-up

Assessment of primary connections between psychosocial impairments, such as depression or apathy, and GHD is not without methodological problems. Increased prevalence of depression and related impairments, such as decreased energy levels, increased emotional lability and social isolation, have been reported in adults with GHD in comparison with healthy controls (1, 15).

The interpretation of these findings is complicated, however, since the non-specific psychological effects of coping efforts due to severe chronic illness cannot be differentiated *a priori* from possible specific biological effects of GHD, which could help to justify substitution treatment. To solve this methodological difficulty, control groups have been introduced. These are control groups with other types of chronic afflictions, such as diabetes, showing increased prevalence of depression

Table 3 Questionnaire results. Values are median (range).

	Males ($n = 44$)	Females ($n = 54$)	Total ($n = 98$)	P
Apathy Scale				
Self report (AS-S)	14 (2–41)	14 (3–36)	14 (2–41)	0.438
Close informant report (AS-I)	14 (4–37)*	13 (4–26)†	13.5 (4–37)‡	0.485
Beck Depression Inventory	6.5 (0–29)	6 (0–34)	6 (0–34)	0.524
List of Somatic Complaints				
Parallel version 1 (LSC)	18.5 (1–57)	22 (0–50)	20.5 (0–57)	0.079
Parallel version 2 (LSC')	18.5 (1–61)	23 (0–61)	20.5 (0–61)	0.164

* $n = 43$, † $n = 49$, ‡ $n = 92$.

Figure 1 Relationship between BDI scores and serum IGF-I values in 98 patients with pituitary diseases; patients with more than two pituitary deficiencies are represented by solid symbols.

Figure 2 Box plots showing medians, inter-quartiles, ranges and outliers of BDI scores grouped by the number of pituitary deficiencies other than GH in all 98 patients with pituitary disease (n = number of patients).

as in GHD (1, 16), or with comparable surgical treatment, e.g. mastoid surgery, which, in contrast, revealed no significant differences in QoL (17). No two diseases are exactly comparable in either the patients' or their environment's perception of the affliction. This may play an important role with respect to psychological impact or the adverse circumstances forced on patients by treatment modalities. Consequently, this approach at best improves on the comparison with healthy controls but does not resolve the problem completely.

A recent study (7) compared groups of patients with GHD, active acromegaly and healthy controls, using the QoL-AGHDA as a psychometric instrument, and found no significant differences in QoL between patients with GHD and elevated GH secretion, making the attribution of QoL-related impairments to GHD conceptually difficult.

Using a similar approach, the present study has examined a group of patients with, as far as the patients' perception of the disease and treatment modalities are concerned, very similar circumstances, but widely varying severity of GHD. This approach should make any specific effects of GHD on the psychological parameters measured stand out clearly when comparing patients with different degrees of GHD within the group. Additionally, a higher degree of GHD would be expected in patients with evidence of psychological impairment in comparison with patients without such evidence, provided the measured impairment is indeed a specific and relevant effect of GHD and not a consequence of the general circumstances of the disease as shared by the whole group.

Questionnaire results

Mean BDI scores in our group of patients (7.51 ± 6.5 ; means $\pm$ s.d.) were slightly higher than those reported by Hautzinger *et al.* (14) for a group of healthy individuals (6.45 ± 5.2), but lower than those of a group of patients with chronic pain (11.7 ± 7.6). Mean LSC scores in this study (21.0 ± 12.5) were slightly above the range reported for healthy groups (mean ranging from 13.5 to 14.1, depending on social group and geographic location) by Zerssen (18), but below those reported for groups of patients with coronary heart disease (30.2 ± 11.8) and various non-psychosomatic diseases (23.7 ± 14). The highly significant correlation between BDI and AS, both of which focus on psychological parameters, and the LSC, which focuses on somatic complaints related to psychosomatic well-being, agrees with the findings reported in the context of the external validation of the LSC (18). It also shows that the patients' self assessments were internally consistent. Evaluation of absolute differences and correlation between AS-I and AS-S provides some external validation of the quality of the patients' self assessment, showing no evidence of a possible lack of insight affecting the quality of self assessment in these patients. This

phenomenon had previously been reported by Peace *et al.* (5) for subgroups of patients with pituitary disease.

Psychometric results and measures of GHD

In our group of patients with pituitary diseases, no relationship between GH status and the severity of psychosocial impairment as measured by the applied psychometric instruments was found. In particular, patients with subnormal IGF-I values or insufficient response in stimulation tests did not differ from the other patients with respect to psychometric results. Power calculations for these group comparisons showed that statistical power is sufficient to exclude, with high probability, levels of depression in the GHD subgroups typical for, e.g., patients with chronic pain (14).

Comparison of patients with little psychosocial impairment and patients with more psychometric evidence of such impairment did not reveal significant differences in GH status. Thus, our study does not support the concept of depression, apathy or reduced psychosomatic well-being as specific symptoms of GHD. The reported improvement of these psychological and psychosomatic symptoms under GH substitution therapy might thus be attributed to secondary effects of somatic improvements induced by GH substitution (3). Consequently, pending further verification of this hypothesis in controlled clinical trials, limiting indication for GH substitution therapy to cases where somatic symptoms of GHD are present in addition to psychological impairments should be considered.

Conclusions

No direct relationship between measures of GHD (IGF-I, GHRHT and ITT as the gold standard in the diagnosis of GHD) and psychometrically measured depression, apathy or psychosomatic well-being was found in the present study. Thus, our observations do not support the concept of depression and related psychological impairments as specific symptoms of GHD, suggesting that improvements of these symptoms under substitution therapy may be indirect effects of somatic improvements, with obvious consequences for the range of valid indications for GH substitution therapy.

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