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ORIGINAL ARTICLE

Effects of previous growth hormone excess and current medical treatment for acromegaly on cognition

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ABSTRACT

Background In untreated acromegaly patients, decreased cognitive functioning is reported to be associated with the degree of growth hormone (GH) and IGF-1 excess. Whether previous GH excess or current medical treatment for acromegaly specifically affects cognition remains unclear. The aim of this study was to compare cognitive functioning of patients who are treated for acromegaly with patients with non-functioning pituitary adenomas (NFA). In addition, we assessed the influence of prolonged medical treatment after initial transsphenoidal surgery on cognition.

Design In this cross-sectional study, 74 patients participated, who were treated for acromegaly (n = 50; median [interquartile range] age: 53 [45–65] years) or NFA (n = 24; age: 63 [59–70] years). The NFA patients were selected for a high likelihood of normal GH secretion based on an IGF-1 z-score within the normal range (> −2) and zero or one axis substituted. Of the acromegaly patients, 28 had achieved remission, while 22 were biochemically controlled with long-acting somatostatin analogues and/or pegvisomant. Memory and executive functioning were assessed by the 15 Words Test and the Ruff Figural Fluency Test, and reported as z-scores.

Results The total patient group scored significantly poorer than the reference population on memory and executive functioning (P < 0·001). However, cognitive test performance was not significantly different between acromegaly patients with a persistent disease, acromegaly patients in remission and NFA patients.

Conclusion The total patient group scored worse compared with reference populations. We found no association between previous GH excess and cognition. In addition, current medical treatment for GH excess in acromegaly was not related to memory and executive functioning.

Keywords Acromegaly, cognition, growth hormone, IGF-1, pegvisomant therapy, somatostatin analog therapy.

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Introduction

Changes in cognitive functioning can be expected as a consequence of growth hormone (GH) excess, or GH deficiency. The reason for this assumption is a wide distribution of binding sites for Insulin-like growth factor-1 (IGF-1) in the brain in particular in the medial temporal lobe (the hippocampus) and in the prefrontal cortex [1]. Indeed, studies on the effects of GH and IGF-1 on cognition performed in GH deficient patients demonstrated a link between GH and cognitive performance, where poor performance was ameliorated with GH treatment [2–4].

In acromegaly, which is characterized by excess GH production, cognitive functioning is also reported to be impaired. In a recent study, Leon-Carrion *et al.* [5] compared patients with active acromegaly with healthy participants. They found a moderate to severe memory impairment in patients and postulated that high levels of GH and IGF-I in acromegaly patients could be the basis for these findings. However, comparisons with untreated acromegaly patients are less informative because nonspecific psychological factors associated with chronic illness will undoubtedly influence the results

[6]. In another study, Sievers and colleagues compared acromegaly patients (of which 60% was either cured or biochemically controlled) with healthy individuals [7]. They found that cognitive dysfunction, particularly attentional deficits, were common in acromegaly. Although this finding is of importance, again comparisons were made with healthy controls. More informative would be a comparison with patients who have non-functioning pituitary adenomas (NFA). These patients share many disease characteristics but do not have the GH excess. This type of study was performed by Tiemensma *et al.* [8], who concluded that there was normal cognitive functioning after long-term cure for acromegaly. The relation of previous GH excess with impaired cognitive functioning remains however controversial due to these inconsistent study results.

In acromegaly, GH and IGF1 may be discordant on medication during persistent disease. Biermasz *et al.* [9] demonstrated that octreotide did not lead to orderly GH secretion in acromegaly in spite of normalization of IGF-1. Neggers *et al.* [10] postulated that long-acting somatostatin analogues normalize serum IGF1 levels in certain patients in the presence of elevated GH actions in extrahepatic tissues. This phenomenon was called extrahepatic acromegaly. This change in diurnal GH profile, while IGF-1 is normalized, potentially also influences cognitive functioning. Until now no research is available on the effects of medical treatment in acromegaly on cognition.

With these considerations in mind, we studied acromegaly patients with persistent disease (i.e. on GH suppressive mediation) and compared them with acromegaly patients who were in remission. In addition, comparisons were made to NFA patients, to investigate the effects of previous GH excess.

Methods and materials

Patients

In this cross-sectional study, patients were recruited for participation at the endocrine outpatient clinic of the University Medical Center Groningen (UMCG), a tertiary referral centre for pituitary surgery in the Netherlands. Inclusion criteria were as follows: age ≥ 18 years, treatment for acromegaly or NFA and regular follow-up in our endocrine outpatient clinic (i.e. at least once a year). Additional in-and exclusion criteria, details of the study protocol and definitions of hormone deficiencies are described elsewhere [11]. Briefly, NFA and acromegaly patients were tested between September 2008 and November 2011. The diagnosis of NFA was based on two criteria: presence of a pituitary macroadenoma (> 1 cm) on magnetic resonance imaging and absence of overproduction of any of the pituitary hormones. The selection of the NFA patients was based on the absence of GH substitution, IGF-1 z-scores within the age-adjusted normal range (> −2) and zero or one axis being substituted. Pituitary deficiencies were defined according to generally accepted guidelines. The initial diagnosis of acromegaly was based on the characteristic clinical signs and symptoms and confirmed by insufficient suppression of GH during an oral glucose tolerance test (oGTT), elevated age-adjusted IGF-1 concentrations and the presence of a pituitary adenoma on radiological imaging. Of the acromegaly patients who were included in this study, 28 were in remission [i.e. they had IGF-1 levels in the normal range, and a normal suppression of GH on oGTT (< 1·0 μg/L)], while 22 had persistent disease and were still treated with long-acting somatostatin analogues and/or pegvisomant. The consecutive approach to our acromegaly study patients was considered to be representative for the patient group, as published previously for NFA patients [12].

IGF-1 assay

Plasma IGF-1 was measured by radioimmunoassay after acid–ethanol extraction (Nichols Institute of Diagnostics, San-Juan Capistrano, CA, USA) [13]. IGF-1 was measured on the day of testing. Data are reported as IGF-1 z-scores.

Cognitive tests

Aspects of verbal memory were assessed with the 15 Words Test (15 WT) which is a Dutch equivalent of the Rey Auditory Verbal Learning Test [14]. In this test, 15 words were presented five times. After each trial, patients were asked to name immediately the words they remembered. This allowed the calculation of three different scores describing *immediate memory*:

1 The *short-term memory score* is based on the number of words patients were able to name after the first presentation of the word list.
2 The *total memory score* represents the total number of words patients remembered over the five trials.
3 The *learning score* describes the difference between the number of words remembered in the third trial in comparison with the first trial.

Besides immediate memory, *delayed memory* was measured.

4 The *delayed memory score* is based on the number of words patients could recall after a period of about 30 min.

Executive functioning was assessed using the Ruff Figural Fluency Test (RFFT) [15]. In this test, patients were presented with sheets of paper on which 35 squares were printed, each with a fixed pattern of five dots. The test consisted of five parts, which differed with regard to the designs. While the configurations of dots are the same in the first three parts of the test, two types of distractions are added in two of these parts. In the last

two parts, the configurations of the dots are different and without distractions. The participant was asked to produce as many different designs as possible by connecting two or more dots in each square with straight lines. The time for each part was restricted to 1 min so that the total test time was 5 min. Responses were scored with regard to the total number of *unique designs* generated over the five parts. The *perseverative errors score* represents the total number of repetitions of the same design drawn. The interrater variability (two independent raters) was determined by Pearson's *r* and was 0·99 for both total unique designs and perseverative errors. The *error ratio* is the total number of perseverative errors divided by the total number of unique designs.

Questionnaires and protocol

A common questionnaire on demographic and health-related data was used with special attention for educational level, social status, full-time/part-time employment, social security benefit, comorbidity, use of medicine, cardiovascular risk factors, traumatic brain injury and dementia. Education level was determined using a Dutch education system, comparable to the ISCED [16]. This scale ranges from 1 (elementary school not finished) to 7 (university level).

The Hospital Anxiety and Depression Scale (HADS) was used to measure symptoms of anxiety and depression and consists of 14 items [17]. Each item is scored as a number, with a maximum score for each subscale (anxiety or depression) of 21. Higher scores indicate more severe anxiety or depression.

In fixed order, the test protocol was as follows: (i) the 15 WT: direct recall, (ii) the RFFT, (iii) a common questionnaire to assess baseline information, (iv) physical examination: length, weight, blood pressure, waist circumference, hip circumference and compliance to the test situation, (v) the HADS and finally (vi) the 15 WT: delayed recall.

The assessment took approximately 40 min and was performed directly after or just before patients' visit to the outpatient clinic. All testing and scoring of tests were performed by trained personnel.

Reference data: healthy control subjects

The performances of patients were compared with Dutch controls. Normative data for the HADS were derived from Spinhoven *et al*. [17]. In this study, general population mean and standard deviations scores were used from 18 to 65 years and > 65 years to calculate z-scores. Reference data for the 15 WT were derived from control subjects of the Maastricht Aging Study (n = 1780, aged 24–81 years) [14]. Regressions models given by the authors were used to determine accurate z-scores. The final test scores were controlled for age, sex and education. Reference data for the RFFT were derived from a sample (n = 10 289, half decades from 20 to 85 years) of the LifeLines Cohort Study [18]. Using the mean and standard deviation scores from this cohort, we standardized our patient scores by converting it into z-scores.

Statistical analyses

The analyses were all carried out using the Predictive Analytics software (PASW; SPSS, Inc., Armonk, NY, USA) statistics 18 package. Demographic data are presented as median and interquartile range (IQR), frequencies or percentages. Normality of data was analysed by QQ-plots. Not all data were distributed normally; therefore, a nonparametric method was used to test for differences between the groups on the cognitive measures. Categorical variables were analysed using chi-squared tests (χ^2 test). Continuous variables were analysed by the Kruskal–Wallis ANOVA. Cognitive performance data were presented as median and IQR. A nonparametric 95% confidence interval (CI) was calculated according to the method of Campbell and Gardner [19]. Furthermore, an impaired performance was defined as a score ≤ 1·3 SD below the normative mean. Only 10% of the overall normal population would be expected to score in this range [20]. We compared three groups: acromegaly patients with persistent disease, acromegaly patients in remission and NFA patients. The two-tailed alpha level of < 0·05 was considered statistically significant. In case of statistical differences between the groups on demographic or cognitive data, a Bonferroni correction was performed to protect against Type I error when performing multiple comparisons. In case of statistical differences between the groups on demographic or cognitive data, Duncan's method was used as a *post hoc* test [21].

Reporting of the study conforms to STROBE statement along with references to STROBE statement and the broader EQUATOR guidelines [22].

Results

Patients

Seventy-four patients participated in the present study (35 men, 39 women, aged 57 ± 12 years, range 22–81 years). Fifty patients with acromegaly and 24 patients with NFA participated. The acromegaly patient group consisted of 22 patients with a persistent disease and 28 patients who were in remission. Patients' characteristics are given in Table 1. The acromegaly patient groups were significantly younger at surgery, radiotherapy and time of testing compared with the NFA patient group. Acromegaly patients with persistent disease activity received significantly more often radiotherapy compared with acromegaly patients who were in remission and NFA patients. Furthermore, time since radiotherapy was longer in acromegaly patients who were in remission compared with acromegaly patients with persistent disease activity and NFA patients. The IGF-1 z-scores were comparable between both

Table 1 Clinical characteristics of acromegaly patients with persistent disease, acromegaly patients in remission and NFA patients

	Acromegaly			
	Persistent disease	**Patients in remission**	**NFA**	***P*-value**
N	22	28	24	
Basic characteristics				
Age (years), median [IQR]	54 [44; 62]	53 [45; 67]	63 [59; 70]	0·008
Sex (males/females)	11/11	12/16	12/12	0·837
Educational level (1/2/3/4/5/6/7)	0/2/0/4/7/7/2	0/2/0/6/12/8/0	0/1/0/5/10/8/0	0·674
Surgery				
Age at surgery (years)				
Median [IQR]	47 [38;56]	43 [36;55]	58 [51;64]	0·002
Average time since surgery (years)				
Median [IQR]	5 [3; 7]	8 [4; 14]	5 [3;9]	0·203
< 1–5 years [number (%)]	50	36	50	0·458
5–10 years	36	25	37	
> 10 years	14	39	13	
Patients with 2nd surgery (%)	18	4	0	0.034
Use of GH suppressive medication				
SA (*N*) (%)	9 (41%)	NA	NA	
Peg (*N*) (%)	6 (27%)	NA	NA	
SA and Peg (*N*) (%)	7 (32%)	NA	NA	
Radiotherapy (RT)				
RT after surgery (%)	64	21	17	0·001
Age at RT (years)				
Median [IQR]	37 [32; 47]	47 [38; 57]	62 [49; 75]	0.046
Average time since RT (years)				
Median [IQR]	4 [2; 7]	16 [11; 24]	4 [2; 4]	0.004
Hormonal substitution				
No. of hormone replacements (0/1/2/3/4/5)	12/5/3/1/1/0	19/6/2/0/1/0	10/14/0/0/0/0	0·070
Glucocorticoid (%)	32	14	17	0·269
Thyroid hormone (%)	27	14	13	0·356
GH (%)	0	7	0	0·379
Sex hormone (%)	18	11	29	0·237
Desmopressin (%)	5	4	0	0·579
IGF-1 z-score				
Median [IQR]	0·42 [−0·43; 0·60]	0·69 [−0·27; 1·17]	−1·12 [−1·56; −0·52]	< 0.001

Table 1 (Continued)

	Acromegaly			
	Persistent disease	**Patients in remission**	**NFA**	***P*-value**
HADS z-score				
Anxiety	0·03 (−0·31; 0·54)	0·25 (−0·03; 0·81)	−0·53 (−1·03; 0·40)	0.038
Depression	−1·14 (−0·73; 0·56)	−0·14 (−0·93; 0·94)	−0·44 (−1·00; 1·04)	0.372

SA, somatostatin analogues, Peg, pegvisomant; GH, growth hormone; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; NFA, non-functioning pituitary adenomas.

acromegaly groups and significantly higher compared with the NFA patient group, despite highly similar hormonal replacements. Both acromegaly patient groups had significantly higher anxiety z-scores (indicating more anxiety) in comparison with the NFA patient group, although there was no indication for clinical anxiety (z-scores within the normal range).

Cognitive tests

Cognitive performance data of the three groups are given in Table 2. The 95% CIs fall below zero for all memory scores and for the unique designs of the executive functioning test. For the same variables, a higher proportion of patients scored in the impaired range (all $P < 0{\cdot}001$).

Z-scores for cognitive functioning in acromegaly patients with persistent disease, acromegaly patients in remission and matched NFA patients are given in Table 3. No significant differences were found in median (IQR) cognitive z-scores between the three groups.

Discussion

In the present study, we found no association between previous GH excess and cognition. In addition, current medical treatment for GH excess was not related to impairments in memory and executive functioning. Although no differences were found between patient groups, most test results differed significantly from the reference populations, indicating a poor cognitive test performance in both patients with acromegaly and NFA.

Only a few studies have addressed cognition in acromegaly. Sievers *et al*. studied 55 patients with biochemically confirmed

Table 2 Cognitive performance of the total patient group

	Median [IQR]	**95% CI of the median**	**Score ≤ 10 perc. *n***	***P*-value***
Memory performance				
15 Words Test				
Short-term memory	−0·36 [−1·29; 0·45]	−0·61; −0·07	18	< 0·001
Total memory	−0·80 [−1·60; 0·33]	−1·00; −0·40	24	< 0·001
Learning score	−0·51 [−1·28; 0·53]	−0·74; −0·03	18	< 0·001
Delayed memory	−0·80 [−1·73; 0·03]	−1·20; −0·30	27	< 0·001
Executive functioning				
Ruff Figural Fluency Test				
Unique designs	−0·52 [−1·51; 0·21]	−0·94; −0·10	22	< 0·001
Perseverative errors	1·02 [0·04; 1·27]	0·76; 1·17	5	0·778
Error ratio	0·73 [0·17; 1·14]	0·61; 0·93	6	0·260

CI, confidence interval; IQR, interquartile range.
**P*-values by chi-squared test comparing the number of patients who score in the impaired range to the number of patients who scored in the unimpaired range.

Table 3 Cognitive performance of acromegaly patients with persistent disease, acromegaly patients in remission and NFA patients

	Acromegaly		NFA	
	Persistent disease	Patients in remission		
	N = 22	*N* = 28	*N* = 24	*P*-value
Memory performance				
15 Words Test				
Short-term memory	−0·74 [−1·69; 0·18]	−0·28 [−0·89; 0·28]	−0·28 [−1·17; 0·61]	0·274
Total memory	−0·85 [−1·63; 0·23]	−0·90 [−1·53; −0·10]	−0·55 [−1·75; 0·60]	0·557
Learning score	−0·03 [−0·65; 1·14]	−0·63 [−1·60; 0·36]	−0·67 [−1·12; 0·48]	0·088
Delayed memory	−0·55 [−1·83; 0·28]	−0·90 [−1·93; −0·10]	0·65 [−1·55; 0·08]	0·714
Executive functioning				
Ruff Figural Fluency Test				
Unique designs	−0·83 [−1·51; 0·00]	−0·29 [−1·42; 0·74]	−0·62 [−1·61; 0·15]	0·538
Perseverative errors	1·05 [−0·32; 1·35]	1·04 [0·04; 1·31]	0·92 [0·26; 1·26]	0·926
Error ratio	0·56 [−0·90; 1·22]	0·80 [0·28; 1·13]	0·67 [0·22; 1·12]	0·691

Cognitive performance data are given as z-scores median [interquartile range].
NFA, non-functioning pituitary adenomas.

acromegaly and compared their data with 87 control subjects. These patients were tested for attention, memory and executive functioning. They found that 33% of the patients had an impaired score (< 16th percentile) in the domain of attention, 24% in the domain of memory and up to 17% in the executive functioning domain. However, no associations between the patient's performance and their status of biochemical control, the current therapeutic regime or the estimated total time of hormone excess, were found [7]. With our more stringent cut-off values (≤ 10th percentile), we also found a high proportion of patients (72%) scoring in the impaired range on at least one outcome variable independent of their status of biochemical control and the current therapeutic regimen. In a study by Leon-Carrion, moderate to severe memory impairment was found in acromegaly patients compared with healthy controls with decreased neural activity in specific brain areas on quantitative electroencephalogram [5]. A different approach to demonstrate altered cognitive function was applied by Tanriverdi *et al.* [23]. In electrophysiological studies, they used the P300 amplitude, which is related to updating of working memory (decision making and memory processing), and found that the mean amplitude at all electrode sites was significantly lower in 18 patients with acromegaly when compared with 16 healthy controls and GH deficient patients. However, the acromegaly patients were enroled into the study before any medical and surgical intervention. Further, as the authors already acknowledged themselves, the skull thickness may have interfered in the measurements of the P300 amplitudes in acromegaly patients.

We decided to compare patients with biochemical control of acromegaly to patients with a pituitary disease but without previous hormone excess. In accordance with the present findings, Tiemensma *et al.* found that cognitive function in patients cured from acromegaly did not differ from patients treated for NFA. Intriguingly and in contrast to a bulk of evidence indicating that any disease (treatment) with its long-term effects results in impairment of cognitive functioning, they found no differences with matched controls [8].

In our study, all but one of the participating patients had normal IGF-1 z-scores. In spite of this metabolic control, acromegaly patients with persistent disease who are on medication are reported to have a disorderly GH secretion with repressed secretory burst-mass and non-pulsatile secretion on octreotide [9]. Another form of discordance is also described between GH and IGF-1 in patients with acromegaly. Neggers *et al.* [10] postulate that long-acting somatostatin analogues normalize serum IGF1 levels in certain patients in the presence of elevated GH actions in extrahepatic tissues. For these reasons, it is very interesting to study the effects of medication in patients with persistent disease and compare them with acromegaly patients in remission. Previously, we demonstrated that quality of life is impaired in association with the need for prolonged postoperative therapy by somatostatin analogues in patients with acromegaly [24]. With regard to cognition, Sonino found no significant improvements in cognition after treatment with octreotide [25] while others found improved cognitive functions [26]. However, both studies assessed self-reported

cognition which is known to be often unrelated to objective measures of cognition [27–29]. Further, within person comparisons were made during active disease and controlled disease, indicating that the effects may not *per se* be related to GH and IGF-1 concentrations. We found no differences between patients with persistent disease and patients who were in remission in spite of far more extensive treatment in persistent disease. This finding suggests that disease control by normalization of IGF-1 alone might be sufficient for improvements in cognitive functioning. This interpretation however remains to be confirmed because our study is cross-sectional in design and therefore limited to infer causality. Additional studies should take GH secretory profiles in these patients into account.

Some limitations need to be addressed. First, we did not use an extensive battery of cognitive tests as is common in many studies on cognitive functioning. We specifically chose for this design to avoid multiple comparisons and thereby potentially inducing type 1 errors. It allowed us also to test a larger group than generally reported in the literature, thereby enhancing our statistical power. However, for future studies an extensive neuropsychological test battery is recommended, where multiple cognitive domains are evaluated. Secondly, baseline and treatment characteristics were at some points different between groups. Although this is an inherent weakness of all observational studies, potential effects have to be taken into account. Previously, we found no negative effects of radiotherapy on quality of life and cognition [11–13]. In regression analysis, we also found no effects of radiotherapy (data not shown).

In conclusion, we found no effects of previous GH excess on cognition. Additionally, acromegaly patients on GH suppressive medication with normal IGF-1 z-scores performed similarly to acromegaly patients who were in remission and NFA patients despite potential differences in diurnal GH concentrations. Based on these findings, the endocrinologist can inform acromegaly patients that memory and executive functioning are not expected to change as a consequence of the GH excess in history or the GH suppressive medication. However, patient groups had poorer cognitive performance corrected for age, and educational level than the reference population, indicating that other disease related factors may potentially be important for cognition. Therefore, more research is needed in the field of cognition in patients with hormonal deficits.

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