Growth Hormone & IGF Research 25 (2015) 47–52

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Acromegaly and aging: A comparative cross-sectional study

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ARTICLE INFO

Article history:
Received 23 September 2014
Received in revised form 9 December 2014
Accepted 11 December 2014
Available online 18 December 2014

Keywords:
Acromegaly
Aging
Geriatrics
Cognitive functions
Dementia
Malnutrition
Physical function
Sarcopenia

ABSTRACT

Objective: Cognitive and functional geriatric assessment may change in acromegaly. Herein we aimed to determine at which points geriatric assessment of the cases with acromegaly differs from that of general elderly population.
Design: In this comparative cross-sectional study, a total of 30 cases with acromegaly (controlled n = 14, uncontrolled n = 16) and 30 gender and body-mass index-matched cases without acromegaly (control group, CG) above 60 years old were included. Cognitive functions were evaluated on the basis of the mini–mental state exam (MMSE). Affective status was determined using the geriatric depression scale. Activities of daily living (ADL) were ranked according to the Barthel index while instrumental activities of daily living (IADL) were graded on the basis of the Lawton scale. Nutritional status was evaluated using the mini–nutritional assessment (MNA). Body composition was measured through bioimpedance analysis. Functional mobility was determined using the Timed Up and Go test (TUG) and muscle strength with the handgrip strength test.
Results: Scores on the MMSE were significantly lower in the elderly cases with acromegaly than in the cases without acromegaly ($p < 0.001$). Dementia was more frequent in the acromegaly group than in the CG ($p = 0.04$). Total MNA scores were significantly lower in cases with acromegaly than in the CG ($p = 0.006$). More subjects in the acromegaly group (33%) were at greater risk of malnutrition than in the CG (3%) ($p = 0.003$). There was greater moderate functional impairment based on Barthel ADL in the acromegaly group than in the CG ($p = 0.04$).
Conclusion: Acromegaly may impair cognitive functions, functional mobility and instrumental daily living activities in the geriatric population. With acromegaly, the risk of malnutrition may also increase.
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1. Introduction

Acromegaly is a persistent, life-long disease. Significant progress in the treatment of the disease has led to increased life-time survival in cases with acromegaly [16]. This has led to concerns about appropriate follow-up of these cases as they age.

GH and IGF-1 normally decrease with advanced age and the decline in both contributes to the aging process and cognitive dysfunction [3,14,30]. However, the impact of acromegaly on changes in GH and IGF-1 axis with aging is controversial [8,31]. Generally, in clinical practice, elderly cases with acromegaly are followed in order to control the disease activity and its complications. However, cognitive and functional geriatric assessment is usually omitted.

Herein, we aimed to evaluate cognitive and functional changes in elderly cases with acromegaly. To our knowledge, this is the first study of its kind to compare geriatric assessment of elderly cases with and without acromegaly.

2. Patients and methods

This cross-sectional comparative study included a total of 30 elderly cases with acromegaly (controlled n = 14, uncontrolled n = 16) above 60 years old. The control group (CG) consisted of 30, randomly chosen age and gender-matched geriatric cases without acromegaly that were followed at the geriatric out-patient clinic.

The study protocol was approved by the Ethics Committee of Cerrahpasa Medical School, Istanbul University. All the subjects read and signed the informed consent forms before enrolling in the study.

2.1. Laboratory evaluation

8-hour fasting blood samples were taken before 10 a.m. to determine the levels of hormones. A chemiluminescence immunoassay was done to determine FSH (Normal: 3.6–12.5 mIU/ml), LH (Normal:

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http://dx.doi.org/10.1016/j.ghir.2014.12.003
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2.4–12.6 mIU/ml), TSH (Normal: 0.4–4.0 mIU/ml), free T4 (Normal: 0.8–1.9 ng/dl), free T3 (Normal: 0.45–3.17 pg/ml), estradiol levels (Normal: 12.5–166 pg/ml) and total testosterone levels (Normal: 0.05–0.82 ng/ml). GH and IGF-I levels were evaluated using one-step sandwich chemiluminescence immunoassay (CLIA) on the Liaison autoanalyzer (DiaSorin, Saluggia, Italy). Cases with acromegaly were considered to have controlled disease activity when they had both circulating IGF-I levels within normal age and gender-adjusted ranges and nadir GH less than 1 ng/ml during oral glucose tolerance test [16].

Fasting blood glucose (FBG) (Normal: 70–110 mg/dl), low-density lipoprotein (LDL) (Normal: 0–130 mg/dl), triglyceride (TG) (Normal: 50–150 mg/dl), insulin (Normal: 0–17 mIU/ml), HbA1c (Normal: 4.8–6%), creatinine (Normal: 0.6–1.2 mg/dl), calcium (Normal: 8.9–10.3 mg/dl), phosphorus (Normal: 2.7–4.5 mg/dl), albumin (Normal: 3.5–5 g/dl), and 25(OH)D vitamin (Normal: ≥30 ug/l) levels were also evaluated for each case. Insulin resistance was calculated by homeostasis model of assessment (HOMA) according to fasting blood glucose and insulin levels. HOMA–IR >2.5 indicated insulin resistance [4].

2.2. Physical examination and assessment of sarcopenia

Fat and muscle mass were assessed by bioimpedance analysis [9]. The free fat muscle mass index (FFMI) was obtained by using Tanita TBF-300 body composition analyzer (Tokyo, Japan). FFMI levels in female cases below 6.42 kg/m^2 and in male cases below 8.87 kg/m^2 were considered to be low [7].

The hand grip strength test for both hands was used to measure muscle strength by using a hand-held isometric dynamometry (Jamar hand dynamometer, Lafayette Instrument Company, USA). The mean of 3 measurements taken at one-minute intervals were used for each case. Hand grip strength was considered to be low when it was below 20 kg in females and below 30 kg in males [19].

The Timed Up and Go test (TUG) was performed to assess the mobility/physical activity and muscular performance of the cases. The time each case took to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down was recorded. Muscle performance was considered to be low when cases completed the task in 15 s or longer [25].

The results obtained from BIA, hand grip strength test and TUG were used to define and stage sarcopenia based on the criteria defined by the European Working Group on Sarcopenia in Older People [10].

2.3. Nutritional assessment

Nutritional status was determined by taking the sum of the scores obtained from short and long forms of the mini–nutritional assessment (MNA) [17]. Scores between 24–30 indicate normal nutritional status, while scores of 23.5–18 and 17 and below point to risk for malnutrition and malnutrition, respectively [17].

2.4. Functional evaluation

Activities of daily living (ADL) of the participants were evaluated on the basis of the Barthel index. The maximum score is 27 points. High scores mean subjects are more dependent when performing activities of daily living [22].

The Lawton scale for instrumental activities of daily living (IADL) was used to appraise more complex activities. The highest total score of the scale is 17. Higher scores show independence in IADL [20].

2.5. Cognitive and psychological assessment

Cognitive impairment was screened by using the mini–mental state examination (MMSE). This is an 11-question inventory which is helpful in screening dementia and in estimating the severity of cognitive impairment. Scores of ≥24 represent normal cognition, while scores of 18–23, 11–17, and ≤10 indicate, respectively, mild, moderate and severe dementia [13].

To identify depression, the short form of the geriatric depression scale (GDS) developed by Yesavage was used. Total scores between 0–4 are considered normal; ones between 5–7 are indicative of minor depression and ones ≥8 are classified as cases of major depression [11,35].

The Acromegaly Quality of Life Questionnaire (AcroQoL) is a disease-specific questionnaire which gauges health-related quality of life in acromegaly. The total score was standardized on a scale running from 0 (worst HRQoL) to 100 (best HRQoL) by using a formula described in the literature [34].

2.6. Statistics

The data were analyzed with the SPSS 17.0 package program. The Chi-square test was used for categorical variables. Sample distribution was evaluated with the Kolmogorov–Smirnov test. Continuous variables with normal distribution were compared by using the Student's test. Continuous variables with non-normal distributions were compared by using the Mann–Whitney U test. The Pearson's correlation coefficient was used for calculation of associations between variables. $p < 0.05$ was considered statistically significant.

3. Results

The mean age was 67.5 ± 6.3 years for the patients with acromegaly and 68.5 ± 6.1 years for the control group ($p = 0.54$). The female/male distribution was 21/9 and 18/12, respectively ($p = 0.4$). There was no difference between the groups in terms of ethnic origin, level of education, income level, marital status and presence of comorbid conditions ($p = 0.1$, $p = 0.2$, $p = 0.08$, $p = 0.5$ and $p = 0.3$, respectively). Use of antidepressant medications was greater in the CG ($p = 0.03$). Tables 1 and 2 contain the demographic data and laboratory findings, respectively, of the two groups.

Table 3 contains the GH, IGF-1 levels, demographic data and the scores for AcroQoL of the elderly cases with controlled and uncontrolled acromegaly. Seven patients (14%) with controlled and 2 patients (44%) with uncontrolled acromegaly had hypopituitarism ($p = 0.08$). Two patients had panhypopituitarism 1 had hypothyroidism and

Table 1
Demographic data of the elderly cases with acromegaly and control group.

	Acromegaly (n,%)	Control group (n,%)	*p*
Origins based on regions			0.1
Eastern	7 (23)	2 (7)	
Western	12 (40)	20 (67)	
Northern	6 (20)	3 (10)	
Southern	1 (3)	0 (0)	
Central	4 (13)	5 (17)	
Educational level			0.2
None	3 (10)	2 (7)	
Low education (<8 years)	23 (77)	18 (60)	
High education (>8 years)	4 (13)	10 (33)	
Income level ($/month)			0.08
<500	11 (37)	17 (57)	
500–2500	19 (63)	11 (37)	
>2500	0 (0)	2 (3)	
Comorbid conditions			0.3
Hypertension	22 (73)	23 (77)	
Diabetes mellitus	9 (30)	6 (20)	
Osteoporosis	3 (10)	3 (10)	
Cardiac	4 (13)	2 (7)	
Cases on antidepressants	3 (10)	10 (33)	0.03*

* Statistically significant p values.

Table 2
HOMA–IR and laboratory findings in elderly patients with acromegaly and control group.

	Acromegaly (n = 30)	Control group (n = 30)	p
Fasting blood glucose (mg/dl)	95 [84–114.5]	92.5 [87–103.8]	0.4
HOMA–IR	1.8 [0.7–3.5]	1.9 [0.6–3.6]	0.6
HbA1c (%)	5.9 [5.6–6.4]	5.7 [5.5–6.1]	0.1
Creatinine (mg/dl)	0.9 [0.7–1]	0.9 [0.7–1]	0.7
Calcium (mg/dl)	9.4 [9.1–9.8]	9.6 [9.4–9.8]	0.3
Phosphorus (mg/dl)	3.5 [3.2–3.7]	3.4 [2.9–3.6]	0.3
Albumin (mg/dl)	4.3 [4–4.5]	4.5 [4–4.7]	0.2
25(OH)Dvit (ug/l)	27 [22.3–34.8]	25.8 [19.1–30.6]	0.8
GH (ng/ml)	0.9 [0.4–1.8]	0.4 [0.2–0.9]	0.03*
IGF–1 (ng/ml)	151.5 [117–267]	123.5 [87.4–159.5]	0.001*
fT3 (pg/ml)	2.6 [2.1–3.1]	2.9 [2.6–3.4]	0.7
fT4 (ng/dl)	1.1 [0.9–1.3]	1.3 [1.1–1.3]	1
TSH (mIU/l)	1.3 [0.4–1.9]	1.7 [0.9–2.7]	0.6
FSH (mIU/ml)	21.5 [9–64.8]	45 [14.5–86]	0.8
LH (mIU/ml)	10 [3.3–24]	17.6 [8.9–29]	0.2
Total testosterone (ng/ml)	331.9 [179–518.8]	396 [355.3–479.8]	0. 4
Estradiol (pg/ml)	11.5 [5–15]	5.9 [5–14.3]	0.2

HOMA–IR homeostasis model of assessment–insulin resistance, GH growth hormone, IGF-1 insulin like growth factor-1, fT3 free triiodothyronine, fT4 free thyroxine, TSH thyroid stimulating hormone, FSH follicle stimulating hormone, and LH luteinizing hormone.
Data was expressed as median and IQR.
* Statistically significant p values.

hypogonadism, 1 had hypogonadism, 3 had central hypothyroidism and 2 had hypocortisolism. They were receiving appropriate hormone replacement therapy.

3.1. Body composition, muscle mass-strength and performance, sarcopenia and nutritional status

The mean body mass index (BMI) tended to be higher in cases with acromegaly (p = 0.05). There was no difference in BIA results between the two groups (p = 0.5). The hand grip strength test, showing the muscle strength was also similar (for right p = 0.2 and for left p = 0.3).

Table 3
Characteristics of the patients with controlled and uncontrolled acromegaly.

	Controlled acromegaly (n = 16)	Uncontrolled acromegaly (n = 14)	p
GH[a] (ng/ml)	0.4 [0.1–0.9]	1.8 [1.3–2.4]	0.001*
IGF-1[a] (ng/ml)	130.5 [91.1–143.7]	271 [162.5–385.8]	0.001*
Duration of diagnosis[a] (month)	120 [20–192]	144 [69–207]	0.7
Treatment of acromegaly (n,%)			
Previous surgery	13 (81%)	10 (71%)	0.5
Radiotherapy			0.4
Conventional	1 (6%)	0 (0%)	
GKR	3 (19%)	4 (29%)	
CKR	2 (13%)	0 (0%)	
Medical treatment			
Somatostatin analogs			0.5
Octreotide-LAR			
10 mg	3 (19%)	0 (0%)	
20 mg	1 (6%)	1 (7%)	
30 mg	5 (31%)	6 (43%)	
40 mg	1 (6%)	1 (7%)	
Lanreotide autogel			
90 mg	0 (0%)	1 (7%)	
120 mg	0 (0%)	1 (7%)	
Cabergoline	3 (19%)	7 (50%)	0.07
Pegvisomant	1 (6%)	0 (0%)	0.3
Associated complications	14 (88%)	13 (93%)	0.6
AcroQoL[a]	80.5 [63.8–92.3]	76.5 [67.8–87.5]	0.9

RT Radiotherapy, GKR Gamma knife radiosurgery, and CKR Cyber knife radiosurgery.
[a] Data was expressed as median and IQR.
* Statistically significant p values.

Table 4
Comprehensive geriatric assessment of the two groups.

	Acromegaly (n = 30)	Control group (n = 30)	p
BMI (kg/m^2)	30.5 ± 5.3	27.5 ± 4.2	0.05
Bioimpedance analysis–FFMI (kg/m^2)	7.9 ± 1.4	7.7 ± 1.2	0.5
Handgrip-strength test-right (kg)	18.6 ± 7.2	16.1 ± 6.3	0.2
Handgrip-strength test-left (kg)	17 ± 7.4	15.2 ± 6.3	0.3
TUG (seconds)	8.8 ± 2.3	8.5 ± 1.9	0.6
Sarcopenia (n,%)			0.1
Absent	23 (82)	18 (60)	
Presarcopenia	4 (14)	11 (37)	
Present	1 (4)	1 (3)	
Mini nutritional assessment-total score	24.7 ± 2.6	26.4 ± 1.7	0.006*
Nutritional status (n,%)			0.003*
Normal	20 (67)	29 (97)	
Risk for malnutrition	10 (33)	1 (3)	
Malnutrition	0 (0)	0 (0)	
Barthel index[a]	0 [0–0.3]	0 [0–0]	0.005*
Basic activities of daily living (n,%)			0.04*
Full function	26 (87)	30 (100)	
Moderate functional impairment	4 (13)	0 (0)	
Severe functional impairment	0 (0)	0 (0)	
Lawton scale[a]	16 [13.5–17]	17 [16,17]	0.07
Instrumental activities of daily living			0.2
Full function	12 (41)	18 (60)	
Moderate functional impairment	17 (59)	12 (40)	
Severe functional impairment	0 (0)	0 (0)	
Geriatric depression scale[a]	4 [3–7]	2.5 [1–5]	0.03*
Depression (n,%)			0.3
Present	12 (40)	8 (27)	
Absent	18 (60)	22 (73)	
Mini mental state exam[a]	24.5 [22–26.3]	29 [28–30]	0.001*
Dementia (n,%)			0.04*
Present	11 (36)	4 (13)	
Absent	19 (64)	26 (87)	

BMI body mass index, FFMI free fat muscle mass index, and TUG timed up and go test.
[a] Data was expressed as median and IQR.
* Statistically significant p values.

There was no difference in TUG results between the two groups (p = 0.6). Likewise, there was no difference between the two groups in terms of the presence of sarcopenia (p = 0.1).

The total MNA score in the acromegaly group was significantly lower than in the CG (p = 0.006). More subjects in the acromegaly group were at risk for malnutrition compared to those in CG (p = 0.003) (Table 4).

The median TUG score was significantly higher in cases with uncontrolled acromegaly than in cases with controlled acromegaly (9 [IQR: 8.5–11] vs. 7.8 [IQR: 6.8–9] seconds, p = 0.02). There were no differences between the groups in BMI, FFMI, hand grip strength test results, presence of sarcopenia or MNA (p = 0.5, p = 1, p = 0.1, p = 0.7, p = 0.2 and p = 0.2, respectively). The number of the cases at risk for malnutrition was also not different when cases with acromegaly were compared on the basis of disease control (p = 0.8).

3.2. Functional status

Table 4 constrains a comparison of functional activity between the cases with and without acromegaly. Barthel ADL was higher in the acromegaly group than in the CG (p = 0.005). More cases with acromegaly had moderate functional impairment, as determined by Barthel ADL (p = 0.04). Lawton scale scores were similar in all groups, albeit it tended to be lower in cases with acromegaly (p = 0.07). There was no difference in the classification of the functional status of the two groups based on IADL (p = 0.2).

Scores for Barthel ADL and Lawton IADL were similar in cases with controlled and uncontrolled acromegaly (p = 0.5 and p = 0.5, respectively).

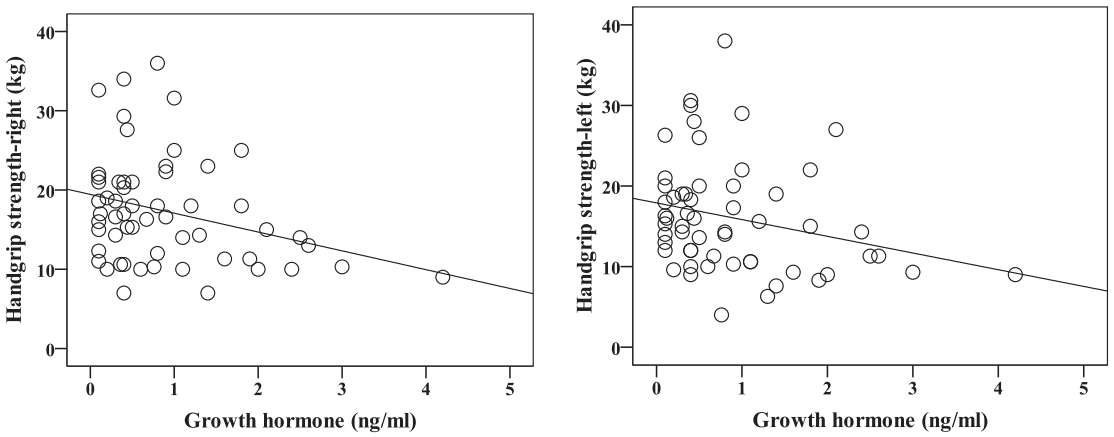

Fig. 1. The correlation of GH levels with the results of hand grip strength test on right and left in the entire group.

3.3. Depression and cognitive functions

Comparison of the scores of GDS and MMSE in cases with and without acromegaly can be seen in Table 4. Acromegaly patients had higher GDS scores compared to the CG ($p = 0.03$). However, the frequency of depression in cases with and without acromegaly was similar ($p = 0.3$).

The score for MMSE was significantly lower in the acromegaly group compared to the group without acromegaly (p 0.001). Dementia was more frequent in cases with acromegaly than in the CG ($p = 0.04$). Seven of the geriatric acromegaly cases (23%) and 4 of the CG (13%) had minimal dementia, whereas 4 of the cases with acromegaly (13%) and none of the CG had a moderate level of dementia.

The GDS in cases with controlled acromegaly was higher than in uncontrolled acromegaly (5.5 [IQR: 3.3–8.8] and 3 [IQR: 1–4.3], respectively, $p = 0.02$). There was no difference in MMSE and AcroQoL scores in the cases with controlled and uncontrolled acromegaly ($p = 0.4$, $p = 0.9$, respectively). The number of the cases with depression or dementia were similar in the two subgroups ($p = 0.1$ and $p = 0.8$).

3.4. Correlations in the entire cohort

Increased GH levels were associated with lower right and left-side hand grip strength test measurements ($r = -0.3$, $p = 0.02$ and $r = -0.3$, $p = 0.05$) (Fig. 1). The score for MNA was not correlated with GH or IGF-1 ($p = 0.5$ and $p = 0.3$).

There was a slight positive correlation between GH levels and Barthel ADL ($r = 0.3$, $p = 0.05$). IGF-1 and BMI were negatively correlated with the Lawton scale, reflecting IADL ($r = -0.3$, $p = 0.04$ and $r = -0.4$, $p = 0.006$).

GDS and MNA scores were negatively correlated in all cases and within the group with acromegaly ($r = -0.5$, p 0.001 and $r = -0.5$, $p = 0.007$). Similarly, in all cases, the MMSE score was negatively correlated with GH, IGF-1 levels and GDS score ($r = -0.3$, $p = 0.03$, $r = -0.4$, $p = 0.004$ and $r = -0.3$, $p = 0.04$, respectively) (Fig. 2).

3.5. Correlations in acromegaly group

In cases with acromegaly, GH levels were negatively correlated with the results of right-hand grip strength test ($r = -0.5$, $p = 0.008$). In addition, TUG scores tended to rise with increasing IGF-1 levels and the time elapsed since diagnosis of acromegaly ($r = 0.4$, $p = 0.06$ and $r = 0.4$, $p = 0.06$). The presence or absence of radiotherapy, pituitary surgery or hypopituitarism in cases with acromegaly did not correlate with FFMI, hand grip strength test of right and left, MNA-total or the presence of sarcopenia (for radiotherapy: $p = 0.9$, $p = 0.5$, $p = 0.1$, $p = 0.3$ and $p = 0.8$, for pituitary surgery: $p = 0.4$, $p = 0.9$, $p = 0.9$, $p = 0.5$ and $p = 0.4$, for hypopituitarism: $p = 0.3$, $p = 0.8$, $p = 0.1$, $p = 0.7$ and $p = 0.3$).

The time elapsed since diagnosis of acromegaly was positively correlated with Barthel ADL ($r = 0.5$, $p = 0.003$). IADL was negatively correlated with BMI ($r = -0.5$, $p = 0.01$). There was no association between the presence or absence of radiotherapy, pituitary surgery or hypopituitarism in cases with acromegaly and TUG and Barthel index or IADL scores (for radiotherapy: $p = 0.3$, $p = 0.7$, $p = 0.3$, for pituitary surgery: $p = 0.5$, $p = 0.2$, $p = 0.4$, for hypopituitarism: $p = 0.7$, $p = 0.4$, $p = 0.4$, respectively).

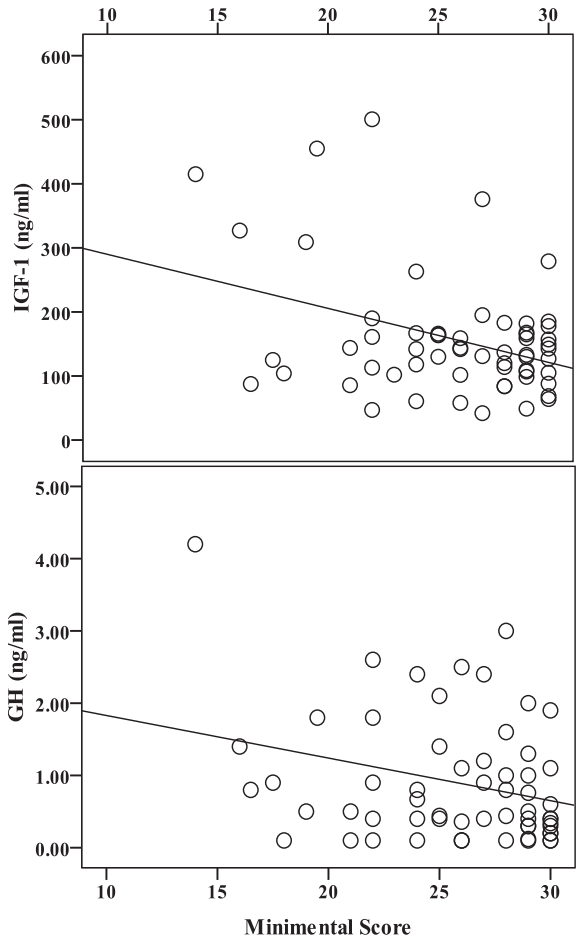

Fig. 2. Correlation of mini–mental scores with GH and IGF-1 levels in the entire group.

Taking into consideration only the cases with acromegaly, there was a slight negative correlation between MMSE scores and GH and IGF-1 levels ($r = -0.3$, $p = 0.08$ and $r = -0.3$, $p = 0.06$, respectively), and a positive correlation between MMSE scores and MNA ($r = 0.3$, $p = 0.02$). MMSE was not correlated with GDS ($p = 0.5$).

AcroQoL was negatively correlated with GDS and positively correlated with scores for Lawton IADL in elderly acromegaly cases ($r = -0.5$, $p = 0.009$ and $r = 0.4$, $p = 0.03$). However, it was not associated with GH or IGF-1 levels or duration of symptoms or diagnosis of acromegaly ($p = 0.6$, $p = 0.5$, $p = 0.3$ and $p = 0.09$).

There was no association between the presence or absence of radiotherapy, pituitary surgery or hypopituitarism and MMSE, GDS or AcroQoL scores (for radiotherapy: $p = 0.9$, $p = 0.1$, $p = 0.4$, for pituitary surgery: $p = 0.2$, $p = 0.4$, $p = 0.9$, for hypopituitarism: $p = 0.6$, $p = 0.7$, $p = 0.2$, respectively).

4. Discussion

In the present study, in the acromegaly group, the median score for the mini–mental test, which reflects cognitive functions, was significantly lower and dementia was more frequent. Increased levels of both GH and IGF-1 were associated with decreased mini–mental scores, meaning excessive GH and IGF-1 levels may contribute to the decline in cognitive functions. The total score for the mini–nutritional assessment was significantly lower in the acromegaly group, thus confirming that poor nutritional status and acromegaly are related. Deficient nutritional status in acromegaly was associated with depression and decreased cognition. In acromegaly, the Barthel index for daily activities of living was significantly higher. This means that the presence of acromegaly may have a negative impact on daily independent activities. Poor scores on the Barthel index, meaning decreased ability to perform basic daily activities independently, were associated with GH, in all subjects, and duration of the disease, in cases with acromegaly. Scores on the Lawton scale were negatively correlated with IGF-1 and body mass index.

Previous studies of geriatric acromegaly have mainly focused on the changes in diagnosis and treatment of the disease that aging demands, by comparing those change to the ones occurring in acromegaly in younger people [8,31]. It is still uncertain, however, how comprehensive geriatric assessment should be adjusted when acromegaly and advanced age coexist. In the present study, the parameters of frequency of sarcopenia and body composition, including FFMI, as reflected by BIA, were the same in the two groups. This suggests that muscle mass in elderly cases with acromegaly may not be different from that in the general geriatric population. Moreover, the results of the hand grip strength test, showing muscle strength, were similar in the two groups. Nevertheless, measurements obtained from the right sided hand grip strength test decreased significantly as GH levels increased in both groups.

Aging results in the reduction of muscle mass, strength and performance, otherwise referred to as sarcopenia, which results in disability in the elderly [10,19]. Moreover, decline in GH and IGF-1 levels with aging has been associated with sarcopenia; however, it is debatable whether improvement is obtained by the replacement of GH or IGF-1 [5,15,23]. Previously, GH administration in healthy aged subjects did not improve muscle strength [5,27]. Loss of pulsatility, rather than actual decrease in levels of GH with age may be responsible for sarcopenia [28]. This may explain why elderly cases with acromegaly in our study did not have improved muscle strength despite having higher GH and IGF-1 levels. Early studies on GH administration and findings of the current study show that excessive GH does not protect muscle strength in elderly, and may even decrease it.

Physical performance of the muscles as assessed by TUG was also similar in the two groups. Although TUG scores were higher in the uncontrolled acromegaly cases than in the controlled ones, the results were within normal range in both groups. Moreover, in our study, there was a slight association between TUG scores and IGF-1 levels and the time elapsed since diagnosis of acromegaly in patients with acromegaly. This means although clinically insignificant, the more prolonged the course of the disease, the greater the detrimental effects on physical performance. This issue should be evaluated in further studies since there are various factors having an impact on physical activity in acromegaly. While increased GH levels are expected to increase physical activity, deformities in acromegaly hinder it [1,33].

Functional assessment has shown moderate functional impairment in elderly cases with acromegaly. The scores on the Barthel index, which is used to assess activities of daily living, were higher in acromegaly group, meaning there were a greater number of cases having moderate functional impairment. In the overall geriatric population, GH levels tended to be positively correlated with the Barthel score. This means that increased GH levels may impair the activities of daily living in the elderly. The functional capacity of instrumental activities in daily living, based on the scores on the Lawton scale, was lower, albeit statistically insignificant, in the acromegaly group. Lower scores on the Lawton scale mean more dependence during performance of instrumental activities in daily living. Both increased IGF-1 levels and higher BMI were associated with impaired functional capacity of instrumental activities. These results may stem from the deformative changes caused by excessive GH and resulting increased IGF-1 [18,33].

Another interesting finding of the current study was the worse nutritional status of the cases with acromegaly compared to that of the general elderly population. Moreover, the cases in the acromegaly group were at greater risk of malnutrition. Nutritional status was not dependent on levels of GH, IGF-1 or the current disease activity. Previously, Fiebrich et al. showed that long-term use of somatostatin analogs lead to a deficiency in fat soluble vitamins [12]. However, in the current study, there was no difference in vitamin D levels between the acromegaly and non-acromegaly groups. Still, together with the findings of Fiebrich et al. our findings show that specialized nutritional support should be provided to elderly cases with acromegaly. Nutrition education should be a part of patient care in the follow-up of cases with acromegaly.

Aging may worsen mood in patients, particularly when they have a chronic disorder [26]. Acromegaly by itself impairs psychological status [2]. In the present study, acromegaly patients had higher GDS scores. Additionally, depression worsened with impaired nutritional status in both the entire group and in the group with acromegaly. This shows that impaired nutritional intake and mood disturbance are related to each other. It is worth mentioning that more cases in the control group were on antidepressants. Nevertheless, there was no difference in frequency of depression, based on GDS scores, in the acromegaly and non-acromegaly groups. In addition, in cases with acromegaly, quality of life was related to depression status and functional status of instrumental activities. Cases having better mood and/or retention of abilities to perform instrumental activities had also better quality of life. However, quality of life was not associated with activity or duration of the disease. AcroQoL was also not related with any of the other parameters evaluated in the current study.

Although previous studies have concluded that decreased GH and IGF-1 levels have a role in loss of cognitive abilities during aging, others have shown that acromegaly itself also has disruptive effects on cognition [3,6,14,21,24,29,30,32]. Similarly in the current study, the MMSE score was significantly lower and dementia was more frequent in the acromegaly group. The MMSE score, reflecting cognitive status, decreased when GH and IGF-1 levels increased. In the entire cohort, MMSE was negatively correlated with GDS, showing cognitive dysfunction was also associated with depression. However, when only cases with acromegaly were taken into consideration, neither the status of disease activity nor depression was directly related to cognitive dysfunction. Additional factors may be involved in cognitive dysfunction in elderly acromegaly cases. One of these factors may be the impaired nutritional status in acromegaly since the score for MMSE was positively

correlated to the score for MNA. In other words, cognitive status improved with better nutritional status.

The current study had certain limitations. First, there was a preponderance of female subjects in both groups, which may have had an impact in our results. However, the relative gender frequency in the two groups was similar, making it possible to compare them. Second, the number of users of antidepressants in the acromegaly group was lower than in the non-acromegaly group. This could be why the depression scores in the two groups were similar. However, this similarity may stem from depression being a confounding factor when comparing the two groups in terms of cognition and malnutrition.

In conclusion, acromegaly may impose an additional burden on cognitive functions, risk of malnutrition, functional mobility and instrumental daily living activities in the geriatric population. A multidisciplinary, more comprehensive approach is necessary for acromegaly cases especially as they age. Follow-up plans for cases with acromegaly should be revised as they get older.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgments

None.

Declaration of interest: The authors declare that they have no conflict of interest.

Funding: This study did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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