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ORIGINAL ARTICLE

Evaluation of depressive mood and cognitive functions in patients with acromegaly under somatostatin analogue therapy

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Abstract
Aims Acromegaly is caused by a pituitary adenoma that releases excess growth hormone (GH) and a concomitant increase in insulin-like growth factor 1 (IGF-1). Acromegaly results not only in phenotypic changes, but also in neurologic complications as peripheral neuropathy and cognitive dysfunction. This study aimed to compare depressive mood and cognitive function in patients with acromegaly and in healthy controls as well as to determine the factors underlying cognitive dysfunction in the acromegalic patients.
Materials and methods This study included 42 patients with acromegaly that were receiving somatostatin analogue therapy and 44 healthy controls. Memory, attention, visuospatial function, inhibitory function, abstract thinking, verbal fluency, and depressive mood were measured in the patients and controls.
Results Patients with acromegaly had lower learning ($p = 0.01$), planning ($p = 0.03$), complex attention and inhibitory function ($p = 0.04$) scores than the controls. There was no significant difference in depressive mood between the patients and controls ($p > 0.05$). Gamma knife radiosurgery did not negatively affect cognitive function ($p > 0.05$).
Conclusion The present findings show that acromegaly negatively affects learning, attention, and planning.

Keywords Acromegaly · Depressive mood · Cognitive functions

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Introduction

Acromegaly is a disease caused by a pituitary adenoma that secretes excess growth hormone (GH). Patients with acromegaly present with enlargement of the extremities, face, and soft tissues, macroglossia and dental changes due to increased GH and insulin-like growth factor 1 (IGF-1) [1–3]. Acromegaly is associated with an increased risk of mortality due to cardiovascular, cerebrovascular disease and intestinal cancer, and an increased risk of morbidity due to diabetes mellitus (DM), osteoarthritis, and obstructive sleep apnea [4]. A recent tool has been proposed to be useful for the diagnosis and follow-up of comorbidities of acromegaly [5].

GH receptors are found in the hippocampus, amygdala, cerebellum, and cerebral cortex [6, 7], and IGF-1 receptors are found in the amygdala, hippocampus, parahippocampal gyrus, and prefrontal cortex [7, 8]. Cognitive function in patients exposed to high levels of these hormones has been the focus of recent research. Studies that compared acromegalic patients and healthy controls reported lower scores in attention, information processing speed, visual and verbal memory, executive function, and decision-making performance in patients [9–13]. Nonetheless, in addition to excess GH and IGF-1, other factors might also play a role in cognitive dysfunction in acromegalic patients.

For instance, white matter lesions are more common in the brains of acromegalic patients and are related to

comorbid vascular risks [14]; however, white matter lesions are not known to be correlated with cognitive function [11]. Moreover, excess GH is associated with increased risk of psychopathology [15]. Acromegalic patients have lifetime prevalence of any mental disorder of 19–64% [16–18], and depression symptoms are reported in 62% of untreated acromegalic patients [9]. Acromegalic patients with high depression and anxiety scores perform poorly on long-term memory and decision-making tests [13]. In addition, the treatment of acromegaly in the form of radiotherapy or surgery, as well as medical therapy, might contribute to cognitive dysfunction [19–21]. The medial temporal lobe and frontal lobe are in close proximity to the pituitary gland, and are exposed to radiation during both conventional radiotherapy (RT) and gamma knife radiosurgery (GKRS) [22, 23].

Adenoma location and surgical treatment have been suggested as possible causes of cognitive dysfunction in acromegalic patients [19, 23]. Pituitary adenoma patients treated with RT following surgical removal of the adenoma are reported to have memory dysfunction [20] and executive dysfunction [21]. GKRS, which projects more beams through the medial temporal lobe and frontal lobe than conventional RT, is thought to cause more severe cognitive dysfunction than conventional RT, although this has not been fully described [22]. Furthermore, acromegaly has a negative effect on quality of life [24–27] and cognitive dysfunction in such patients might be a contributing factor [10]. The present study aimed to compare depressive mood and cognitive function in acromegalic patients receiving somatostatin analogue (SSA) therapy and in healthy controls, as well as to determine the factors underlying cognitive dysfunction in the acromegalic patients.

Materials and methods

Study population

Seventy patients with acromegaly, who were admitted to the Endocrinology and Metabolism Outpatient Clinic of Marmara University School of Medicine, from January 2014 to January 2015, were invited to participate in the study. Inclusion criteria for the patient group were age 18–65 years, a diagnosis of acromegaly, and use of SSA therapy for the treatment of acromegaly. Volunteers between the ages of 18 and 65 years constituted the control group. Exclusion criteria for the patient and control groups included any disease that could interfere with cognitive function and any comorbidity that could preclude patients from completing the study tests. During the recruitment period and cognitive evaluation, the investigators assessing the cognitive function did not know whether the disease was in a controlled state or not in the acromegalic patients.

Among the 70 acromegalic patients, 15 chose not to participate in the study, 5 were excluded due to a diagnosis of cancer (colorectal cancer: $n = 3$; breast cancer: $n = 2$), 2 were excluded due to a comorbidity that could affect cognitive function (epilepsy: $n = 1$; Parkinson's disease: $n = 1$), 1 patient was excluded due to a history of head trauma, and 2 diagnosed with dementia and 1 with mild cognitive impairment were also excluded. Two patients were further excluded during the analyses due to insufficient data. DM or other vascular risk factors were not considered exclusion criteria. The study was completed with 42 acromegalic patients and 44 healthy controls. The controls those were of similar age and education level as the patients were recruited from among hospital staff and their families.

Acromegaly was diagnosed based on a high serum IGF-1 level when compared to appropriate reference levels for age and gender and an uncontrolled GH level (<1 ng mL^{-1}) following oral glucose tolerance test (OGTT). Serum GH and IGF-1 levels were also measured in the controls. Normal reference IGF-1 values for age and gender were used [2]. All patients had a pituitary adenoma. Both patients and healthy controls were evaluated cross-sectionally. Patients were assessed based on history and physical examination. Body weight, height, and systolic and diastolic blood pressure were measured in all the patients. Postoperative laboratory findings, pituitary function test results, type of treatment for acromegaly (transsphenoidal surgery, craniotomy, GKRS, conventional RT, and medical therapy), and pituitary hormone replacement were ascertained from the patients' medical records.

The study protocol was approved by the Marmara University School of Medicine Ethics Committee and all the participants provided written informed consent. The study was carried out in accordance with the Declaration of Helsinki, and was supported by the Marmara University Research Foundation (SAG-C-TUP-120613-0245).

Assessment of cognitive function and depressive mood

Cognitive evaluation in both groups was performed in the morning between 09:00 am and 11:00 am. Cognitive assessments were performed 7–10 days after the OGTT. Verbal memory and learning were measured using the Oktem Verbal Memory Scale (OVMS), a validated and standardized Turkish word list test similar to the Rey Auditory Verbal Learning Test [28, 29]. OVMS is widely used in other studies [30, 31] and is a reliable tool to assess verbal memory in Turkey. OVMS is administered in 2 parts. For the first part, a 15-word list is presented 10 consecutive times, and respondents must repeat as many words as

possible (a test of immediate verbal memory). The second part is administered 30 min after the first part, and respondents must repeat as many words from the 15-word list as possible (a test of delayed memory). The learning score is the total number of words a subject can learn after 10 repeats, regardless of they are repeated in the same run or not. Maximum learning score is the maximum number of words that can be remembered in one repeat.

The digit span forward and backward subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) were used to test working memory [32]. Although newer versions of this scale (WAIS III and IV) are available in multiple languages, WAIS-R is the only version that is validated for use in the Turkish population. Participants are required to repeat a series of digits in the same order for the digit span forward test and in the reverse order for the digit span backward test.

Attention was tested using the Trail Making Test (TMT) A; participants must draw lines to connect 25 consecutive encircled numbers (1–25). Executive function, planning, working memory, and visual scanning were measured using TMT B [33], which requires participants to draw lines to connect alternating sequential numbers and letters in alphabetical order (1-A, 2-B to L-13). Visuospatial function was tested using the clock-drawing test; participants are asked to draw a clock and the clock should be contained in a circle or rectangle, the numbers should to be placed appropriately, and the clock arms should indicate the time as 11:10.

Inhibitory function, interference, and focused attention were tested using the Stroop Color and Word Test (SCWT) [34]; the version used has 5 steps. For step 1, participants read words written in black, for step 2 they read the words written in color (blue, red, yellow and green), for step 3 they identify the color of circles, for step 4 they identify the colors of words, and for step 5 they identify the colors of words written in a different color (e.g., blue written in red). The time to complete each step is recorded. Inhibitory function is tested during step 5, and the time difference between step 5 and each step (the Stroop effect) is scored. Abstract thinking was tested using the similarities subtest of WAIS-R [32]; participants must express what 2 presented items have in common in an abstract sense (e.g., orange and banana; fruit).

Phonological and semantic subgroups of verbal fluency were tested using the Controlled Oral Word Association Test, which requires participants to identify as many animals as possible in 1 min (semantic fluency) and as many words as possible starting with the letters K-A-S consecutively (phonological fluency). The Beck Depression Inventory (BDI) was used to assess depressive mood [35]. This inventory has 21 items regarding depressive mood; each item is scored as 0–3 and higher scores indicate greater severity of depressive mood. All the tests were administered by H.A. or Basak N. Gokceimam, who are experienced administering neuropsychological tests. The battery of tests was completed in approximately 45 min without a break.

Biochemical evaluation

Venous blood samples were collected between 08:00 a.m. and 09:00 a.m. following 10–12 h of fasting. A 75-g OGTT was performed. Blood glucose and GH levels were measured at 0, 30, 60, 90, and 120 min. Nadir GH was defined as the lowest GH obtained at any time point during the 2-h OGTT. Acromegalic patients with a nadir GH level >1 ng dL^{-1} were considered uncontrolled [2].

The serum GH levels were measured using a solid-phase, 2-site chemiluminescent immunometric assay and an automated analyzer (IMMULITE 2000, Siemens, USA). The intra-assay coefficient of variation was 3.5–4.2% for a concentration range of 2.6–17 ng mL^{-1} and the total inter-assay coefficient of variation was 6.5–6.6%. Analytic sensitivity was 0.01 ng mL^{-1} and the measureable range was 0.05–40 ng mL^{-1}.

The serum IGF-I levels were measured using a solid-phase enzyme-labeled chemiluminescent immunometric assay and an automated analyzer (IMMULITE 2000, Siemens, USA). The intra-assay and inter-assay coefficients of variation were 3.9–2.4% for a concentration range of 77–1358 ng mL^{-1} and the total intra-assay coefficient of variation of was 7.7–4.7%. Analytic sensitivity was 20 ng mL^{-1} and the upper end of calibration was 1600 ng mL^{-1}.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.20 (IBM Corp., Armonk, NY, USA). Numerical variables were expressed as mean ± SD and categorical variables as percentage. The Chi square test was used to compare categorical variables. The Shapiro–Wilk normality test was used to determine the normality of the distribution of continuous variables. For normally distributed continuous variables, the parametric Student's *t* test was used. For non-normally distributed continuous variables, the non-parametric Mann–Whitney *U* test was used. Pearson's and Spearman's rank correlation coefficients were used to analyze 2 continuous variables. The level of statistical significance was set at $p < 0.05$.

Results

Mean duration of acromegaly was 7 years (range 1–28 years). In all, 41 (97.6%) of the acromegalic patients had undergone surgery to remove a pituitary adenoma. Six (14.6%) of those 41 patients had recurrent surgery. Among the patients, 3 (7%) received conventional RT and 22 (52.4%) were treated using GKRS. All the patients were receiving SSA therapy at the time of the study. In total, 17 (40.5%) patients had concomitant DM, 16 (38.1%) had hypertension (HT), 15 (35.7%) had hyperlipidemia, 14 (33.4%) had hypogonadism, 7 (16.7%) had adrenal insufficiency, and 5 (11.9%) had panhypopituitarism. Three (7%) of the diabetic patients were using insulin and the rest were on oral anti-diabetic medication. Blood glucose levels were under control in all acromegaly patients.

Patients vs. controls

Patient and control demographics are shown in Table 1. Mean age in the patients group was 42.9 ± 9.3 years (range 20–61 years), versus 39.7 ± 6.9 years (range 25–52 years) in the control group. The serum GH and IGF-1 levels in both groups were normal. Learning scores were significantly lower in the patient group than in the control group (OVMS learning score: $p = 0.01$; OVMS maximum learning score: $p = 0.04$). After completion of 10 repeats, 30.2% of the patients and 52.3% of the controls were able to correctly repeat all 15 OVMS words ($p = 0.04$). There were no significant differences in other OVMS part 1 and 2 scores between the patient and control groups (OVMS short-term memory: $p = 0.13$; OVMS long-term memory: $p = 0.17$).

Patient attention, planning, and visual scanning scores based on TMT A and B were significantly lower than those of the controls (TMT A: $p = 0.03$; TMT B: $p = 0.04$). Patient and control group scores for visuospatial function, inhibitory function, interference, focused attention, abstract thinking, and verbal fluency did not differ significantly. Additionally, BDI scores did not differ significantly between the 2 groups. Cognitive test and BDI results in both groups are shown in Table 2.

Acromegalic patients

Coexistent DM, HT, and hyperlipidemia were present in 17 (40.5%), 16 (38.1%), and 15 (35.7%) of the patients, respectively. Acromegalic patients with DM, HT, and hyperlipidemia were significantly older than those without these comorbidities ($p = 0.03$, $p = 0.03$, and $p = 0.04$, respectively).

In total, 65% of the acromegalic patients were classified as controlled using the criteria specified. The uncontrolled acromegalic patients had insuppressible GH levels, based on OGTT and high IGF-1 levels. The uncontrolled group consisted of more recently diagnosed patients ($p = 0.04$). Other variables, including age, gender, DM, HT, hyperlipidemia, and laboratory values other than GH and IGF-1 did not differ between the controlled and uncontrolled patients (Table 3).

Patients with DM had significantly lower OVMS short-term memory, TMT B, and WAIS-R similarities subtest scores than those without DM ($p = 0.01$, $p = 0.04$, and $p = 0.002$, respectively). Patients with HT had significantly lower Stroop test scores ($p < 0.05$ for all Stroop scores). BDI scores did not differ significantly between the controlled and uncontrolled acromegalic patients ($p = 0.56$). Furthermore, BDI score was not correlated with any of the cognitive test scores ($p > 0.05$, for all cognitive test scores). The biochemically controlled patients did not perform better than the uncontrolled patients on the cognitive tests and had lower learning and long-term memory scores (Fig. 1).

As the duration of disease increased, the BDI score decreased ($p = 0.03$, CC = −0.334). Time to complete TMT B was positively correlated with disease duration ($p = 0.04$, CC = 0.331); TMT B performance decreased as the duration of disease increased. Duration of disease did not have any effect on other test results. In all, 21 (50%) of the patients were treated using GKRS. There were no differences in cognitive function test scores between the patients that were and were not treated using GKRS, but BDI scores were significantly lower in patients treated with GKRS ($p = 0.04$).

Table 1 Demographics of patient and control group

	Patient ($n = 42$)	Control ($n = 44$)	p
Age (mean ± SD)	42.9 ± 9.3	39.7 ± 6.9	0.75
Gender (F/M)	23/19	25/19	0.75
Hand preference (R/L)	38/4	42/2	0.43
Education (years)	8.23 ± 3.8	7.93 ± 2.9	0.88

Discussion

The present findings show that learning, attention, and planning scores were lower in acromegalic patients receiving SSA therapy than in healthy controls matched for age, gender, and level of education. The present findings are in agreement with earlier reports of attention deficit [11, 19] and learning disability [11, 12] in acromegalic patients. On the other hand, in contrast to previous reports [9, 10, 13], no difference was found in memory function between acromegalic patients and controls in the present study. In previous studies, patients with acromegaly had worse memory scores [9, 10, 13]. However, in these studies, the patients also had worse mood scores. The mean BDI score in the present study's acromegalic patients was similar to that

Table 2 Cognitive test scores and Beck depression scale results of patients and controls (all scores are depicted as mean ± SD)

	Patient	Control	*p*
OVMS learning			
Learning score	12.53 ± 2.3	13.59 ± 1.9	0.01*
Maximum learning	12.91 ± 2.0	14.00 ± 1.4	0.04*
OVMS memory			
Short-term memory	5.44 ± 1.7	6.11 ± 1.9	0.13
Long-term memory	14.19 ± 1.5	14.43 ± 1.2	0.17
Trail making			
A form: time (s)	63.50 ± 38.7	42.34 ± 13.3	0.03*
A form: number of mistakes	0.09 ± 0.5	0.18 ± 0.4	0.32
B form: time (s)	119.84 ± 58.0	93.63 ± 34.7	0.04*
B form: number of mistakes	0.50 ± 1.3	0.80 ± 1.4	0.29
Stroop Color-Word Test			
Stroop time (s)	37.06 ± 16.9	34.16 ± 12.6	0.47
Stroop mistakes (number)	1.63 ± 2.3	1.36 ± 2.3	0.30
Stroop effect	18.75 ± 14.4	19.10 ± 10.3	0.45
Verbal fluency			
Semantic fluency	19.38 ± 5.4	20.16 ± 4.5	0.13
Phonologic fluency: *K* (time: s)	11.21 ± 4.6	12.32 ± 5.2	0.30
Phonologic fluency: *K* (number of repeats)	0.29 ± 0.8	0.43 ± 1.0	0.46
Phonologic fluency: *K* (number of mistakes)	0.05 ± 0.2	0.07 ± 0.2	0.69
Phonologic fluency: *A* (time: s)	7.48 ± 5.0	8.91 ± 5.0	0.19
Phonologic fluency: *A* (number of repeats)	0.17 ± 0.5	0.32 ± 1.1	0.42
Phonologic fluency: *A* (number of mistakes)	0.0 ± 0.0	0.02 ± 0.2	0.33
Phonologic fluency: *S* (time: s)	7.05 ± 4.3	8.70 ± 4.0	0.71
Phonologic fluency: *S* (number of repeats)	0.14 ± 0.5	0.18 ± 0.5	0.71
Phonologic fluency: *S* (number of mistakes)	0.02 ± 0.1	0.16 ± 0.6	0.19
Digit span			
Forward	5.42 ± 1.3	5.41 ± 1.6	0.97
Backward	4.3 ± 1.8	4.9 ± 2.0	0.14
Beck Depression Scale	10.24 ± 8.5	10.43 ± 7.0	0.62
Clock drawing	3.63 ± 0.8	3.84 ± 0.4	0.12
Similarities	13.07 ± 6.0	14.02 ± 4.5	0.71

Data are presented in mean ± standard deviation

* $p < 0.05$

reported previously [9] but it did not differ from that in the present study's controls. Therefore, reported mood difference between patients and controls in the literature could be the reason for worse memory detected in those patients.

In the present study, acromegalic patients with DM had lower short-term memory, executive function, and abstract thinking scores than those without DM, and patients with HT had lower executive function scores than those without HT. However, the patients that had these 2 comorbidities were significantly older than those that did not, which, together with their vascular risk factors, might have played a role in their lower scores. Imaging studies have shown that cognitive dysfunction in acromegalic patients is independent of vascular risk factors and subsequent white matter lesions [11]. Cranial imaging findings caused by vascular risk factors were not evaluated in the present study; therefore, any conclusions about the effects of vascular risk on cognitive function in the present study's acromegalic patients would be purely speculative.

Biochemically controlled patients in the present study had lower long-term memory scores than those that were uncontrolled, which can seem counterintuitive; however, the controlled patients had longer duration of disease than the uncontrolled patients and, consequently, may have had elevated GH and IGF-1 levels for a longer period of time. It is not known for how long the controlled or uncontrolled state ensues. The patients were designated as controlled or uncontrolled based on just one laboratory test.

Table 3 Demographics and laboratory values of controlled and uncontrolled patients

	Controlled ($n = 28$)	Uncontrolled ($n = 14$)	p
Age	44.7 ± 8.8	39.36 ± 9.9	0.83
Gender (F/M)	16/12	7/7	0.66
Disease duration (months)	92.1 ± 75.6	56.29 ± 75.5	0.04*
HT (%)	9 (32.1)	7 (50.0)	0.30
DM (%)	11 (39.3)	6 (42.9)	0.90
HL	10 (35.7)	5 (35.7)	0.75
GH (ng dL^{-1})	0.96 ± 1.1	16.5 ± 29.9	0.028*
IGF-1 (ng mL^{-1})	147.3 ± 54.6	510.2 ± 215.5	<0.001*
Fasting blood glucose (mg dL^{-1})	107.0 ± 49.1	101.7 ± 22.9	0.70
Hba1c (%)	5.52 ± 0.9	5.20 ± 1.7	0.60
TSH (μU mL^{-1})	1.24 ± 0.86	1.16 ± 0.70	0.79
fT4 (pg mL^{-1})	1.01 ± 0.52	0.83 ± 0.22	0.22
LH (IU L^{-1})	7.55 ± 7.6	4.28 ± 5.7	0.07
FSH (mIU mL^{-1})	25.80 ± 69.3	6.44 ± 9.8	0.06

Categorical data are presented in number (percentage) and numerical data are presented in mean ± standard deviation

HT hypertension, *DM* diabetes mellitus, *HL* hyperlipidemia, *GH* growth hormone, *IGF-1* insulin-like growth factor-1, *TSH* thyroid stimulating hormone, *fT4* free T4, *LH* luteinizing hormone, *FSH* follicle stimulating hormone

* $p < 0.05$

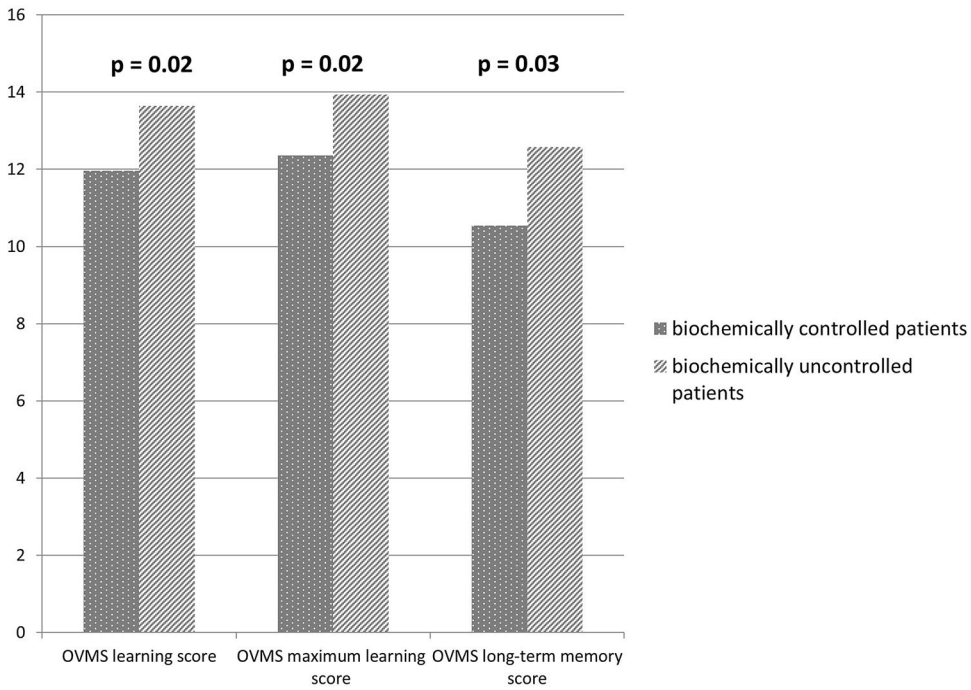

Fig. 1 OVMS scores in the biochemically controlled and uncontrolled acromegalic patients. *OVMS* Oktem Verbal Memory Scale

Although in daily practice, control status of the disease and treatment strategy can be decided depending on a single GH and IGF-1 value, for research purposes, one value may not be adequate to establish disease control. Time spent without treatment, i.e., exposure to excessive GH and IGF-1, is known to negatively affect memory [9, 10]. The present findings relevant to controlled and uncontrolled acromegalic patients should be considered with caution, as the number of uncontrolled patients was quite small. Newly diagnosed patients in the present study were less likely to be under biochemical control and had higher BDI scores. As BDI scores in the controlled and uncontrolled patients were similar, depressive mood in the newly diagnosed patients was most likely not related to the uncontrolled

state of the disease, but might have been a reaction to a newly diagnosed disease.

The medial temporal lobe and frontal lobe, which are in close proximity to the pituitary gland, are exposed to radiation during both RT and GKRS. With GKRS, a larger area of healthy brain tissue is exposed to a lower dose of radiation than with conventional RT [36]. The effects of RT have been studied [11, 12, 19–21, 37–39], and there are a few reports of the negative effects of RT on memory function [20, 37]. GKRS is preferred over conventional RT in our hospital, and only 3 of the present study's patients received conventional RT; therefore, the effect of RT was not analyzed. The fact that 93% of the patients did not receive RT may be why memory deficit was not observed, which was reported in other studies [9–11].

Although GKRS is hypothesized to cause cognitive dysfunction in pituitary adenoma patients, the only relevant study failed to show such an effect [22]. That study was criticized because of its heterogeneous patient population and small sample size [40]. In the present study, GKRS did not have an observable effect on cognitive function in the acromegalic patients.

The most important limitation of the present study is its cross-sectional design, which precludes identifying causality. Furthermore, the small sample limited the ability to perform multiple comparison analysis while controlling for such factors as DM, HT, and controlled versus uncontrolled disease state. Despite the fact that, the present study population was small, it is comparable to other similar studies. Mean duration of education in the present study was low (i.e., 8 years), but was similar in the patient and control groups. Although patient and healthy controls were not matched for age, sex and education level, these demographics were similar in both groups. Another limitation is that acromegalic patients were not compared to patients with another chronic disease. Chronic disease itself is known to cause cognitive dysfunction [41]. When compared with non-functional pituitary adenoma (NFPA) patients, acromegalic patients had similar cognitive scores, but both groups had lower scores than healthy controls [12], but NFPA patients in this study are significantly older than those with acromegaly. Another study that compared cognitive function in NFPA and acromegalic patients [15] reported impaired attention in the acromegalic patients, as in the present study. Additionally, it would have been interesting to compare patients with controlled acromegaly and those with controlled DM in terms of cognitive function. Lastly, the effect of concomitant hypothyroidism, panhypopituitarism, hypogonadism, and diabetes insipidus on cognitive dysfunction and depressive mood in the acromegalic patients could not be analyzed due to the small sample.

In the present study, the BDI was used to assess depressive mood. This inventory is designed to measure the severity of depression and is not a tool for diagnosis. Furthermore, psychopathologies other than depression have been reported in acromegalic patients [15]. The present study did not include detailed psychiatric evaluation in order to limit the duration of cognitive assessment and increase participant compliance.

Conclusion

The most important cognitive functional impairments in the present study's acromegalic patients were learning, attention, and inhibition. Additional prospective studies with larger samples are needed to further understand cognitive dysfunction and its causes in acromegalic patients.

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Compliance with ethical standards

Conflict of interest The authors declare there is no conflicts of interest—financial or otherwise—related to the material presented herein.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (SAG-C TUP-120613-0245).

Informed consent All subjects gave informed consent for participation.

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