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ORIGINAL ARTICLE

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Sleep disorders and cognitive dysfunction in acromegaly

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Abstract

Purpose In the general population, sleep disorders are associated with an increased risk of cognitive impairment. The prevalence of sleep disorders, such as sleep apnea, in acromegalic patients is higher than in the general population, and they may have additional risk of cognitive impairment due to acromegaly treatment and comorbidities. We aim to study the relationship between sleep disturbances and cognitive dysfunction in a group of acromegalic patients.

Methods We studied 67 consecutive acromegalic patients. We performed a neurocognitive assessment and patients completed the Acromegaly Quality of Life Questionnaire (AcroQoL), Epworth Sleepiness Scale, and Pittsburgh Sleep Quality Index.

Results Of the 67 acromegaly patients in the study, 38.8% were male and median age at the neurological examination was 56 (IQR 48, 65). Approximately 6–10% of patients had impaired cognitive assessment, depending on the test. In linear regression models adjusted for age, sex, BMI, disease duration, and disease activity, poorer sleep quality was associated with lower global cognitive z-score ($B = -0.03$, 95% CI -0.06, -0.002). Daytime somnolence was associated with poorer physical AcroQoL sub-score ($B = -0.04$, 95% CI -0.08, -0.002). Sleep quality was associated with poorer overall AcroQoL ($B = -0.03$, 95% CI -0.05, -0.006), physical AcroQoL ($B = -0.04$, 95% CI -0.07, -0.005), psychological AcroQoL ($B = -0.02$, 95% CI -0.04, -0.001), and social AcroQoL ($B = -0.02$, 95% CI -0.04, -0.0009).

Conclusions In acromegaly patients, we found robust evidence that poor sleep quality is associated with poorer quality of life, and some evidence that it is associated with poorer cognitive function.

Keywords Growth hormone · Acromegaly · Sleep · Cognition · Quality of life

Introduction

Acromegaly is a rare chronic disease and it is frequently due to a pituitary-increased secretion of growth hormone (GH) that causes an increased hepatic production of insulin growth factor-1 (IGF-1). GH and IGF-1 excess cause a systemic involvement with multiple comorbidities and increased mortality in patients with active disease. In the literature, it has been shown that acromegalic patients are at risk of cognitive dysfunction [1], and there is also evidence of an increased incidence of dysexecutive syndrome [2], impaired verbal and visual memory and language disabilities [3]. In acromegaly, cognitive dysfunctions are described in naïve patients but also in patients with active and controlled disease, and these findings can persist even in cured disease [1–3]. It is also well known that acromegalic patients have MRI-measured volumetric and white matter changes that correlate with cognitive performance dysfunction [3]. In these patients, the increased risk of

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cognitive impairment is due to GH and IGF-1 excess, cardio- and cerebrovascular comorbidities, an increased incidence of depressive mood, and acromegalic treatment, such as radiotherapy [4–6].

Acromegaly patients are also at increased risk of developing sleep-disordered breathing (SDB), because they have increased GH and IGF-1 levels and enhanced somatostatin tone, which negatively affect breathing [7]. Obstructive sleep apnea (OSA), one of the most common comorbidities in acromegaly [8], is associated with snoring, fragmented sleep, poor sleep quality, daytime somnolence, morning sleepiness, reduction of quality of life, and increased mortality and morbidity [9].

The association between SDB and cognitive decline and risk of dementia has been well documented [10]. In the general population, 60–70% of people with dementia or cognitive impairment had sleep disturbances that cause an increased risk of mortality. Conversely, sleep disturbances, such as quality and duration of sleep, and sleep disorders, such as SDB and sleep behavior disorder, are associated with a higher risk of cognitive impairment and dementia [11]. In acromegaly, there are several studies about SDB [12–14], but there is a paucity of studies about other sleep disruption. Moreover, data about the relationship between sleep disorders and cognitive dysfunction in acromegaly are scant. With this study, we aim to go investigate the link between sleep disruption and cognitive dysfunction in a group of acromegalic patients.

Methods

Patients

We enrolled 71 consecutive acromegalic patients followed at outpatient service of Clinica Medica III at the Department of Medicine of Padua University Hospital. We proposed the evaluation when patients came to our outpatient clinic for blood tests or endocrinological evaluation. We invited 72 consecutive patients. Inclusion criteria were: diagnosis of acromegaly, ≥18 years old, and able to understand the study and give informed consent. Exclusion criteria were: patients that did not give their consent to the study, the inability to do tests and questionnaires, and presence of any other pathological condition or laboratory test which, in the opinion of the investigator, could compromise patient safety. We studied 67 patients because four patients did not give their consent to the study, and we excluded 1 patient with major depression, because they were unable to complete the tests and questionnaires. Diagnosis of acromegaly was based on high IGF-1 and GH levels, MRI findings, and patient clinical documentation.

In clinic, we collected: age at diagnosis, years of active disease, GH and IGF-1 values (at diagnosis and at neurocognitive and sleep assessment), adenoma size, previous acromegaly treatment (neurosurgery, radiation treatment, medical treatment), acromegaly medical treatment at sleep evaluation, characteristics, and treatment of pituitary deficit (at diagnosis and at sleep assessment), BMI, comorbidities (glucose metabolism impairment, hypertension, dyslipidemia, cardiomyopathy, arrhythmia, bone disease, bone pain, OSA, and cerebrovascular disease), concomitant psychiatric disorder, and potential neuroleptic treatment. Patients suspected of OSA through clinical evaluation and self-report then completed polysomnography to confirm the diagnosis, consistent with acromegaly guidelines [15]. All patients with pituitary deficits were in good balance with pituitary hormone replacement therapy at the time of sleep and cognitive assessment. This study was approved by the University of Padua ethical committee. Written informed consent was obtained from all patients.

Sleep questionnaires

Patients completed the following self-administered questionnaires: Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI). The ESS measures daytime somnolence. Patients are asked to rate on a scale of 0–3 how likely they would be to doze off or fall asleep in eight situations based on their usual way of life (such as sitting and reading, watching TV) [16]. Individuals with ESS scores above 10 are considered excessively sleepy [15].

The PSQI measures sleep quality over the previous month. Seven clinically derived domains of sleep (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction) are assessed by the questionnaire [17]. Taken together, these sleep domains are scored as a single factor of global sleep quality [18]. Individuals PSQI scores above 5 are considered to be poor sleepers [18]; the questionnaire has a sensitivity of 89.6% and specificity of 86.5%.

Neurocognitive assessment

We administered a neurocognitive assessment of major cognitive domains, including measures of memory, visuospatial abilities, attention and executive function, and verbal ability. The neurocognitive assessment was conducted by a neuropsychologist from Clinica Medica III in the Department of Medicine at the University Hospital of Padua, Italy in a quiet room, in a single session.

The Short Story Recall Test was used for the assessment of verbal long-term memory [19]. The story, containing 28 items, was read aloud by the examiner. Immediate and

delayed verbal recall was evaluated using the number of correct reproduced items as performance measure. Verbal short-term memory and working memory were assessed using the Digit Span forwards and backwards tests, respectively [19]. The examiner pronounced digits at a rate of 1 s, and required patients to repeat a series of digits in the same order for the digit span forwards test and in the reverse order for the digit span backwards test.

Visuospatial short-term and working memory were evaluated using the Corsi Block-Tapping test forwards and backwards, respectively [20]. The examiner tapped a sequence of blocks, which the patient repeated in the correct and reverse sequential order. The Rey–Osterrieth Complex Figure Test (ROCF) [21] was used for the evaluation of visuospatial constructional ability and visual memory First, the patient was given the ROCF stimulus card, and then asked to draw the same figure (copy). Subsequently, they were instructed to draw what they remembered (delayed recall), after a delay of ~20 min.

Selective attention, cognitive flexibility, and sensitivity to interference were tested using the short version of the Stroop Color Word Test [22]; the version used has three steps. First, the patient reads word written in black, then they identify the color of circle (red, blue, and green), and, finally, they identify the colors of words written in different colored fonts (e.g. red written in blue).

Frontal Assessment Battery (FAB) [23] is a short cognitive and behavioral six-subtest battery: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. The global performance on these six subtests gives a composite score summarizing the severity of the dysexecutive syndrome.

Trail-Making Test (TMT-A; TMT-B) [24] requires the subject to connect, as quickly as possible, 25 consecutive targets distributed over a sheet of paper. TMT-A examines attentional speed, while TMT-B is a measure of executive control and attention. In part A, encircled numbers have to be connected consecutively by drawing lines (1–25) and, in part B, numbers and letters have to be connected consecutively by alternating between numbers and letters in numerical and alphabetical order.

Verbal fluency tests [25], both phonological and semantic cue, were tested. These tasks require the patient to identify as many animals, fruits, and brands of cars as possible in 1 min (semantic fluency) and as many words as possible starting with the letters F-L-P (phonological fluency).

Cut points to define normal range have been established for each test by the scoring guidelines. Raw scores were converted into scaled scores, considering age and education of each patient for each test with a normative sample comparison. If patients scored below these cut points, they were considered cognitively impaired.

Quality of Life Questionnaire

Patients completed the Acromegaly Quality of Life Questionnaire (AcroQoL) [26], a 22-item questionnaire scored on a Likert scale (1–5). The global score is the sum of the 22 items, its maximum score is 110 (scored as a percentage) and it reflects the highest possible AcroQoL. We also analyzed the following subscales: (1) physical aspects score (8 items), (2) psychological aspects score (14 items), (3) physical appearance score (7 items), and (4) disease burden on patients' personal relationships score (7 items). Physical appearance and disease burden AcroQoL sub-scores are derived from the overall psychological sub-score [27].

Statistical analysis

Patient characteristics and clinical variables were summarized. We created cognitive test domain *z*-scores for four domains: memory (digit span forward, Short Story Recall—immediate and delayed); executive function/attention (digit span backward, Stroop, and TMT); visuospatial (Rey Figure copy and recall, and Corsi block span); verbal fluency (semantic and phonological). We additionally created a global *z*-score combining these domains and *z*-scored FAB. We utilized linear regression models to investigate the association between sleep (ESS and PSQI) and cognitive test performance. We additionally examined the association between sleep and quality of life measures, which were log-transformed to create more normal distributions. Model 1 was unadjusted; Model 2 was adjusted for age, sex, BMI, duration of acromegaly, and acromegaly activity at the exam.

Results

Participant characteristics and clinical variables are presented in Table 1. Mean clinical follow-up duration in these patients was 12 years. Three patients were naïve patients, three patients were untreated because they were on reevaluation after neurosurgery treatment, and three patients were untreated because they were cured by neurosurgery treatment. A total of 57 patients were on medical treatment: 25 patients with first generation somatostatin analogs (SRL), seven patients with Pasireotide, 14 patients with Pegvisomant (PEG), and 11 patients were on combined treatment (SRL plus dopamine-agonist, DA,: three patients, SRL plus PEG: four patients, PEG plus DA: one patient, PEG plus Pasireotide LAR: three patients).

Table 1 Participant characteristics, median (IQR), or *N* (%)

Male	26 (38.8)
Age at acromegaly diagnosis	45 (35, 53)
Age at neuropsychological exam	56 (48, 65)
BMI	27.2 (24.1, 31.4)
Disease duration at acromegaly diagnosis (years)	30 (11, 42.5)
IGF-1 (ng/ml) at acromegaly diagnosis	813.5 (626, 959)
IGF-1 (ng/ml) at neuropsychological exam	198 (161, 245)
Adenoma size	
Macroadenoma	15 (23.8)
Microadenoma	47 (74.6)
Empty sella	1 (1.6)
Number of surgeries	
0	15 (22.4)
1	42 (62.7)
2	9 (13.4)
3	1 (1.5)
Radiotherapy	6 (9.0)
Number of pituitary deficits at acromegaly diagnosis	
0	56 (84.9)
1	9 (13.6)
2	1 (1.5)
Number of pituitary deficits at neuropsychological exam	
0	45 (70.3)
1	11 (17.2)
2	5 (7.8)
3	3 (4.7)
Disease activity at psych exam	
Cured	3 (4.5)
Active	27 (42.2)
Disease controlled with medical treatment	34 (50.8)

BMI body mass index, *IGF-1* insulin-like growth factor-1

Patients had a median 3.5 (interquartile range [IQR] 1, 5, range 0–8) comorbidities. Bone pain (58.2%), hypertension (56.7%), and hyperglycemia (50.8%) were, respectively, the three most common comorbidities. Four (6%) patients had diagnosed OSA. Six patients had depression diagnosis and six were on neuroleptic treatment. No patients had diabetes insipidus at the time of diagnosis and 2 (3.1%) had diabetes insipidus at the neuropsychological exam. The median ESS score was 5 (IQR 2, 8), and the median PSQI score was 6 (IQR 4, 9). Most participants performed within the normal range of cognitive tests, however, ~6–10% were impaired, depending on the test. Participants had a median AcroQoL overall score of 68.2 (IQR 54.5, 79.5), and scored the lowest in the physical appearance sub-score (median (IQR) 4.0 (3.6, 4.3)). Participant cognitive test performance and AcroQoL scores are reported in Table 2.

In linear regression models examining the association between sleep and cognitive test performance among acromegaly patients, we did not find strong evidence of an association (Table 3). Unexpectedly, greater daytime somnolence, as measured by the ESS, was associated with better visuospatial *z*-scores in model 1 ($B = 0.05$, 95% CI 0.009,

Table 2 Participant sleep questionnaires, cognitive test and QoL scores, median IQR, or *N* (%)

Sleep questionnaires	
PSQI	6 (4, 9)
ESS	5 (2, 8)
Cognitive tests	
Z Memory	−0.004 (−0.63, 0.47)
Z Executive function	−0.19 (−0.34, 0.19)
Z Visuospatial	0.09 (−0.46, 0.44)
Z Verbal ability	−0.13 (−0.47, 0.59)
Z Global FAB	0.09 (−0.19, 0.26)
Corsi forward cut point	
Deficit	0 (0)
Impaired	5 (7.5)
Corsi backward cut point	
Deficit	5 (7.5)
Impaired	1 (1.5)
Digit forward cut point	
Deficit	4 (6.0)
Impaired	4 (6.0)
Digit backward cut point	
Deficit	4 (6.0)
Impaired	7 (10.5)
TMT A cut point	
Deficit	1 (1.5)
Impaired	1 (1.5)
TMT B cut point	
Deficit	1 (1.6)
Impaired	1 (1.6)
TMT A/B cut point	
Deficit	1 (1.6)
Impaired	4 (6.4)
Short story recall, immediate cut point	
Impaired	14 (20.9)
Short story recall, delayed cut point	
Impaired	15 (22.4)
AcroQoL scores	
Overall AcroQoL	68.2 (54.5, 79.5)
Physical AcroQoL	4.1 (3.8, 4.4)
Psychological AcroQoL	4.2 (4.0, 4.4)
Physical appearance AcroQoL	4.0 (3.6, 4.3)
Social AcroQoL	4.5 (4.2, 4.5)

PSQI Pittsburgh Sleep Quality Index, *ESS* Epworth Sleepiness Scale, *FAB* Frontal Assessment Battery, *TMT* Trail-Making Test, *AcroQoL* Acromegaly Quality of Life Questionnaire

Table 3 Linear regression models examining the association between PSQI/ESS and cognitive test *z*-scores

	ESS		PSQI Global	
	B (95% CI)	*p*	B (95% CI)	*p*
	Model 1			
Z Memory	0.009 (−0.04, 0.06)	0.724	−0.02 (−0.06, 0.04)	0.633
Z Executive Function	0.00004 (−0.04, 0.04)	0.998	−0.01 (−0.05, 0.02)	0.442
Z Visuospatial	0.05 (0.009, 0.09)	**0.019**	−0.01 (−0.05, 0.03)	0.659
Z Verbal Ability	−0.02 (−0.08, 0.03)	0.400	−0.03 (−0.08, 0.03)	0.307
Z Global	−0.01 (−0.04, 0.02)	0.503	−0.03 (−0.05, 0.002)	0.069
	Model 2			
Z Memory	0.008 (−0.05, 0.07)	0.776	−0.01 (−0.06, 0.04)	0.688
Z Executive Function	−0.003 (−0.04, 0.04)	0.872	−0.03 (−0.06, 0.007)	0.110
Z Visuospatial	0.05 (0.002, 0.10)	**0.043**	−0.002 (−0.05, 0.05)	0.934
Z Verbal Ability	−0.02 (−0.08, 0.05)	0.603	−0.02 (−0.08, 0.04)	0.508
Z Global	−0.007 (−0.04, 0.03)	0.666	−0.03 (−0.06, −0.002)	**0.037**

Model 1 unadjusted. Model 2 adjusted for age, sex, BMI, disease duration, disease activity at psych exam, Results statistically significant are in bold

ESS Epworth Sleepiness Scale, *PSQI* Pittsburgh Sleep Quality Index

Table 4 Linear regression models investigating the association between PSQI/ESS and log AcroQoL scores

	ESS		PSQI	
	B (95% CI)	*p*	B (95% CI)	*p*
	Model 1			
Overall AcroQoL	−0.03 (−0.05, −0.002)	**0.032**	−0.03 (−0.05, −0.003)	**0.027**
Physical AcroQoL	−0.05 (−0.08, −0.02)	**0.003**	−0.04 (−0.07, −0.005)	**0.023**
Psychological AcroQoL	−0.02 (−0.04, 0.007)	0.182	−0.02 (−0.04, 0.002)	0.078
Physical appearance AcroQoL	−0.03 (−0.06, 0.008)	0.136	−0.03 (−0.06, 0.005)	0.096
Social AcroQoL	−0.01 (−0.03, 0.008)	0.263	−0.02 (−0.03, 0.002)	0.076
	Model 2			
Overall AcroQoL	−0.02 (−0.04, 0.01)	0.241	−0.03 (−0.05, −0.006)	**0.015**
Physical AcroQoL	−0.04 (−0.08, −0.002)	**0.038**	−0.04 (−0.07, −0.005)	**0.023**
Psychological AcroQoL	−0.004 (−0.03, 0.02)	0.758	−0.02 (−0.04, −0.001)	**0.038**
Physical appearance AcroQoL	−0.01 (−0.05, 0.03)	0.587	−0.03 (−0.06, 0.0007)	0.055
Social AcroQoL	−0.002 (−0.02, 0.02)	0.858	−0.02 (−0.04, −0.0009)	**0.040**

Model 1 unadjusted. Model 2 adjusted for age, sex, BMI, disease duration, disease activity at psych exam, Results statistically significant are in bold

AcroQoL Acromegaly Quality of Life Questionnaire

0.09) and model 2 ($B = 0.05$, 95% CI 0.002, 0.10). In addition, poorer sleep quality, as measured by the PSQI, was associated with poorer global *z*-score ($B = -0.03$, 95% CI −0.06, −0.002).

In linear regression models examining the association between sleep and AcroQoL, we found daytime somnolence, as measured by the ESS, was associated with poorer overall AcroQoL ($B = -0.03$, 95% CI −0.05, −0.002) and physical AcroQoL ($B = -0.05$, 95% CI −0.08, −0.02) in unadjusted models (Table 4). After adjusting for covariates, this association remained significant only for the physical AcroQoL sub-score ($B = -0.04$, 95% CI −0.08, −0.002). Sleep quality, as measured by the PSQI, was associated with poorer overall AcroQoL ($B = -0.03$, 95% CI −0.05, −0.003) and physical AcroQoL ($B = -0.04$, 95% CI −0.07, −0.005) in unadjusted models. These associations remained statistically significant after adjustment (overall: $B = -0.03$, 95% CI −0.05, −0.006; physical: $B = -0.04$, 95% CI −0.07, −0.005), and we found a statistically significant association with psychological AcroQoL ($B = -0.02$, 95% CI −0.04, −0.001) and social AcroQoL ($B = -0.02$, 95% CI −0.04, −0.0009).

We additionally conducted several sensitivity analyses, because several factors may differentially affect sleep, cognition, and/or quality of life among acromegaly patients, as it does not have a homogenous treatment course. First,

we examined whether ESS and PSQI cut points were associated with cognitive test performance. Normal ESS scores are below 10 [16] and normal PSQI scores are below 5 [18], therefore, we used these as our initial cut points. However, because few patients scored higher than 10 on the ESS, we additionally examined the median (5) as the cut point, as well. However, we did not find any association between sleep and cognition using these dichotomous cut points as predictor variables. In addition, we examined several potential effect modifiers using interaction terms, including status of acromegaly (controlled vs. active), treatment of pituitary hormonal deficits, IGF-1 level (continuous and normal range values), radiotherapy, number of deficits, number of comorbidities, and BMI (<30 kg/m^2 and <25 kg/m^2), but did not find that any of these were effect modifiers. Further, we additionally adjusted for hypertension, because it is associated with both quality of life and cognition, but found it did not significantly affect the outcomes. Finally, using logistic regression models, we examined whether sleep was associated with impaired cognitive performance (i.e., below normal cut points, to be considered a deficit), but also found it was not.

Discussion

In this study, we examined the association between sleep quality and daytime somnolence and cognitive test performance and AcroQoL in 67 acromegaly patients. We did not find a strong association between poorer sleep quality over the past month and poorer cognition. Daytime somnolence, instead, was associated with poorer physical and overall AcroQoL and poorer sleep quality was associated with poorer physical, social, psychological, and overall AcroQoL. These findings suggest that even relatively young acromegaly patients (median age at exam 56 years) may have cognitive impairment when compared with the general population, but its relationship with sleep disorders in this population is still missing. Instead, not surprisingly, poorer sleep seems to negatively affect AcroQoL in this population.

In this heterogeneous population, cognitive impairment prevalence (6–10%, depending on the test) was similar to what has previously been reported in the literature. Some past studies have shown that acromegalic patients had an increased incidence of cognitive dysfunction [1], dysexecutive syndrome [2], and a reduction of learning planning, complex attention, and inhibitory functions [5]. Acromegalic patients may have cognitive impairment in every phase of disease: before diagnosis, after surgery, and, even if medical and surgical treatments can improve directly and indirectly brain function, cognitive impairment can persist in long remission period, as well [27–29]. These findings explain the cognitive impairment presence even in young acromegalic patient populations [29].

Regarding sleep disorders, acromegalic patients have an increased incidence of SDB [9]. In the literature, OSA prevalence is between 20 and 80%, with a higher incidence compared with the general population both before diagnosis and after neurosurgery treatment. SDB and OSA in the general population have been associated with cognitive decline and risk of dementia [10]. In addition, SDB is associated with other sleep disturbances, including snoring, fragmented sleep, poor sleep quality, daytime somnolence, and morning sleepiness. The association between sleep disturbances and cognitive decline has been widely documented [11], but, to our knowledge, this is the first study examining the association between sleep and cognition in acromegaly patients. Pituitary surgery, regardless of disease control and disease remission, may reduce the incidence of OSA in acromegalic patients [14]. In this population, OSA is mainly due to a direct GH and IGF-1 action on upper airway narrowing and to an indirect enhanced somatostatin tone effect on central breathing centers [7]. In our study, OSA prevalence (6%) was lower than what has previously been reported in the literature, probably because 58% of our patients had a medical treatment controlled (patients on SRL treatment: 57%, patients on PEG treatment: 33%) or cured disease. It is also well known that SRL and PEG treatment efficaciously improve central and obstructive causes of OSA [30, 31]. Moreover, in our sample, many participants are women, while older age and male gender are associated with increased risk of OSA. In addition, in the general population hypothyroidism and hypogonadotropic hypogonadism may be involved in development of OSA and obesity is a major risk factor for OSA; however, in our cohort all patients with pituitary deficits were well compensated with hormonal replacement therapy and only 30% of patients had a BMI higher than 30 kg/m^2 [12, 32].

In our study, we found patients with cognitive impairment but found only a weak relationship with sleep disruptions, probably because we had a lower incidence of OSA. Moreover, in this study population, cognitive dysfunction may be related with high incidence of cardiovascular and metabolic comorbidities (hypertension 56.7%, hyperglycemia 50.8%) and longer disease duration (median time from diagnosis and cognitive assessment 11 years).

However, we found strong evidence that poorer sleep quality and diurnal somnolence were associated with poorer quality of life scores. A reduced quality of life in acromegalic patients is mainly due to locomotor dysfunction (pain and physical performance), body image alteration, radiotherapy side effects, and active disease. From these data, we can infer that sleep disruption in acromegaly is probably not caused only by SDB but also by other sleep disorders, such as insomnia, circadian rhythm disorders, parasomnias,

sleep-related movement disorders, and sleep-related headaches [4, 33–36]. Interestingly, daytime somnolence was associated only with poorer physical AcroQoL sub-score, while sleep quality was associated with poorer physical, psychological, and social AcroQoL sub-scores. In our population, 58% of patients had bone pain, 24% took more than five concomitant drugs, and six patients had a diagnosis of depressive disorder, all of which may contribute to sleep disruption.

This study has multiple strengths, including the relatively large sample of acromegaly patients, the extensive cognitive battery and quality of life measures, and the novelty of the investigation of the association between sleep and cognition in this population, but there are also limitations that must be considered. First, there were a limited number of patients ($N = 4$) with OSA in our sample, which, given that SDB is quite common in acromegaly, may not be entirely representative of the larger patient population. Second, although our sample ($N = 67$) is comparable with other acromegaly studies, future studies in larger cohorts, with greater power and generalizability are needed to further investigate the association between sleep and cognition and quality of life. Finally, although self-reported sleep has been associated with cognition [37], objective measures of sleep (e.g., actigraphy and polysomnography) would provide further information about the association of sleep and cognition and quality of life in acromegaly.

This study provides evidence for a weak association between sleep disruption and cognition, and a more robust association between sleep and quality of life, in acromegaly patients. Poorer cognition seems to be outside of the risk of SDB—one of the most common comorbidities in acromegaly. These findings indicate that clinicians should be aware of the impact that sleep disruption has on quality of life of their acromegaly patients. Beyond being aware of the risk of SDB in acromegaly, clinicians should assess and monitor sleep disturbance in their patients. Because sleep is a modifiable risk factor, it can be intervened upon to decrease risk of poor quality of life in acromegaly.

First, it should be noted that acromegaly treatment can lead to resolving of SDB [15]. Medical and surgical acromegaly treatment can resolve OSA in these patients. However, if OSA persists, it should be treated with continuous positive airway pressure [38]. Both pharmacological (e.g., z-drugs) and nonpharmacological (e.g., cognitive behavioral therapy and bright light therapy) have been shown to be effective for treating other sleep disorders, including insomnia [38]. Clinicians may also find it beneficial to review patient's diets (e.g., caffeine and alcohol consumption) and medications, as these may also negatively impact sleep [38]. By monitoring sleep and offering treatment strategies when necessary, clinicians may improve sleep in acromegaly patients and, thereby, ameliorate the negative effects sleep disruption has on cognition and quality of life. In addition, future studies are needed to further examine the initial evidence presented here. Longitudinal studies in larger samples of acromegaly patients will provide further insight into the association between sleep disturbances—both within and beyond SDB—and cognition and quality of life.

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Compliance with ethical standards

Conflict of interest The authors do not have any conflicts of interest to report.

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