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PSYCHIATRIC DISORDERS AND ANGER IN PATIENTS WITH CONTROLLED ACROMEGALY.

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ABSTRACT:

Introduction: acromegaly is a chronic rare disease caused by a pathological increase in growth hormone (GH) secretion. In acromegaly an increased prevalence of psychiatric disorders has been demonstrated, in particular depressive disorders, associated to a significant deterioration of the quality of life, independently from disease control. In addition, anger feelings, often detected in subjects affected by chronic disease, have not yet been investigated, in pituitary patients.

Aim of study was to evaluate in acromegaly patients with a controlled disease, compared to patients suffering for non-functioning pituitary adenoma (NFPA), a) prevalence of depressive and anxiety disorders and b) expression and control of anger feelings. The second outcome was to evaluate the correlation between psychiatric disorders, anger feelings and the need for a medical treatment to control the disease in acromegaly group.

Methods: This is a cross-sectional, observational study, which included 53 patients enrolled at the Neuroendocrinology Outpatient Clinic of "City of Health and Science of Turin". Of the 53 enrolled patients (24 male and 29 female), 34 had acromegaly (ACRO), while 19 had non-functioning pituitary adenoma (NFPA), as control group. All subjects completed the following self-administered, validated psychological tools: SF-36 (Short-Form 36 Item); STAXI – 2; BDI-II (Beck Depression Inventory – II); STAI (State-Trait Anxiety Inventory). Only in acromegaly group, patients completed PASQ (Patient-Assessed Acromegaly Symptom Questionnaire) and ACROQoL (Acromegaly Quality of Life Questionnaire) questionnaires. In addition forty-five patients underwent the International Neuropsychiatric Short Interview to assess the presence of a psychiatric disorder. For each patient, anthropometric, clinical and biochemical information were collected.

Results: a higher frequency of psychiatric anxiety and mood disorders (not reported in the medical history) was observed in patients with controlled acromegaly. In the SF-36 questionnaire, a lower score was found in the “emotional well-being” items in ACRO compared to NFPA, particularly in

those with cured acromegaly. Cured acromegalic patients had a worsen score in "emotional well-being", "energy / fatigue" and "general health" items. Finally, subjects in acromegaly group obtained a lower score in the ability to control anger and a higher score in the physical expression of it, demonstrating a tendency to more aggressive behaviors.

Conclusion: this study showed that psychiatric illness is often hidden in patient suffering from acromegaly, despite normal IGF-I levels. Recovery from the disease, as well as not needing treatment, do not necessarily improve QoL scores, in fact in cured patients the quality of life can be even worse.

INTRODUCTION:

Acromegaly is a chronic rare disease caused by a pathological increase growth hormone (GH) secretion. It has an incidence of 4 million people every year, but in apparent increase in recent years [1, 2], characterized by higher mortality compared to the general population. A GH-secreting pituitary adenoma is the prevailing cause. Acromegaly is a systemic disease characterized by alterations of the acral and facial features, hyperhidrosis, headache, sleep apnea, arthropathy, sexual dysfunction, arterial hypertension, thyroid goiter and multiple cardiovascular, metabolic and systemic complications. The improvement in the medical, surgical and radiotherapy treatments has led to a better management of the disease and, consequently, to reduction of mortality. However, often, the hormonal control does not allow to control all the symptoms because elevated hormonal levels for a long time determine irreversible organic alterations[3]. In fact, in acromegaly patients an increased prevalence of psychiatric disorders has been demonstrated, in particular of depressive disorders, independently of the compensation of illness [4–6] with consequent significant deterioration of the quality of life. However, studies with appropriate methodology aimed to detect the prevalence and severity of depressive symptoms or depressive disorders in patients with acromegaly population are very few. On the other hand, an association between chronic disease and depressive and anxiety

disorders as well as between chronic disease and anger is already been demonstrated [7]. Moreover, depressive symptoms could manifest itself with aggressive behavior. Nowadays, it is not clear whether the increased prevalence of depressive disorders is attributable to the effect of chronic increase in GH and Insulin-like Growth Factor (IGF-I) on brain morphology/function or to a psychological reaction to a severely debilitating, chronic condition, which involves a deep alteration of body image. The only study conducted in this regard [5] found that the age of onset of depressive disorder predates the age of acromegaly diagnosis, in support of the first hypothesis mentioned above. While there are data documenting a significant deterioration in the quality of life of patients suffering from acromegaly, to date no studies are available that have investigated the relationship between acromegaly, depression and anger.

Based on that, the main aim of our study was to evaluate in acromegaly patients with a controlled disease, compared to patients suffering for non-functioning pituitary adenoma (NFPA) a) prevalence of depressive and anxiety disorders and b) expression and control of anger feelings. The second outcome was to evaluate the correlation between psychiatric disorders, anger feelings and the need for a medical treatment to control the disease in acromegaly group.

METHODS:

This was an observational cross-sectional study, including 53 patients enrolled in the outpatient Neuroendocrine Clinic of the "City of Health and Science of Turin" University Hospital (Turin, Italy). The participation in the study was offered to all acromegalic and non-functioning patients (control group) examined during outpatient visits between January 2019 and February 2020. Inclusion criteria were: 1) age >18 years, 2) diagnosis of acromegaly or non-functioning pituitary adenoma 3) written informed consent, 4) for acromegaly patients a documented control of disease. Exclusion criteria were: 1) language barrier; 2) history of active cancer diagnosis other than pituitary one; 3) active acromegaly disease and 4) a known psychiatric disorder diagnosis. During the outpatient visit, all subjects completed the following self-administered, validated psychological tools: SF-36 *(Short-*

Form 36 Item); STAXI – 2; BDI-II *(Beck Depression Inventory –II*); STAI *(State-Trait Anxiety Inventory*). Only in acromegaly group, patients completed PASQ *(Patient-Assessed Acromegaly Symptom Questionnaire)* and ACROQoL *(Acromegaly Quality of Life Questionnaire*) questionnaires. All questionnaires were completed on the same day. The patient had an outpatient room and a doctor available to answer any questions or clarifications on how to fill in the questionnaires. In order to assess prevalence of psychiatric disorders according to DSM-5, patients and control underwent through M.I.N.I. (Short International Neuropsychiatric Interview) [8], a short structured face to face interview. This tool has been validated in Italian and has been shown to have excellent reliability and validity characteristics. Additional data were documented by the physician regarding anthropometric and clinical features and regarding acromegaly status with definition of disease activity: "*controlled* acromegaly" (IGF-I levels lower than upper limit of normality for age, under treatment) or "cured acromegaly" (IGF-I levels lower than upper limit of normality for age and no need of any further treatment). Hormonal control and healing were defined according to consensus guideline recommendations [9]. The number of medical consultations and visits in the previous year were also recorded, including any kind of specialist visit, consultations for medication or visits due to new complaints.

Data are presented as median (first and third quartiles) for skewed variables and mean and standard deviation for normal distribution variables. Statistical analysis was performed using the MedCalc™ program (version 18.11.3). The case and control groups were compared using the Mann-Whitney U test for continuous variables and using the chi-squared and Fisher tests for categorical variables. Multivariate analysis was performed using a logistic regression model, after logarithmic transformation of all variables with a skewed distribution. A p-value <0.05 was considered statistically significant. The study was approved by the local ethical committee. All patients gave written informed consent.

QUESTIONNAIRES:

1) **PASQ questionnaire (Patient-Assessed Acromegaly Symptom Questionnaire)** is a specific tool to evaluate symptoms of patients suffering from acromegaly. It includes seven items: headache, perspiration, joint pain, fatigue, soft tissue swelling, numbness or tingling of limbs (item 1–6) and an overall perceived health (‘‘general physical condition’’) score (item 7). Scores can be given from 0 to 8 for item 1–6 and from 0–10 for item 7 (maximal score 58). In general, lower PASQ scores indicate better health or fewer or less severe symptoms.

2) **ACROQoL questionnaire (Acromegaly Quality of Life Questionnaire)**: AcroQoL score can be analysed globally (22 questions with a 5-point Likert scale for each item), or separating physical (eight items) and psychological domains (14 items, subdivided into appearance and personal relations sub-domains, with seven items each). Comparable results are reported in all available languages [10].

3) **STAI questionnaire** is a tool to measure via self-report the presence and severity of current symptoms of anxiety and a generalized propensity to be anxious. There are two subscales within this measure. First, the State Anxiety Scale (S-Anxiety) evaluates the current state of anxiety, asking how respondents feel “right now,” using items that measure subjective feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system. The Trait Anxiety Scale (T-Anxiety) evaluates relatively stable aspects of “anxiety proneness,” including general states of calmness, confidence, and security. The STAI has 40 items, 20 items allocated to each of the S-Anxiety and T-Anxiety subscales. Responses for the S-Anxiety scale assess intensity of current feelings “at this moment”: 1) not at all, 2) somewhat, 3) moderately so, and 4) very much so. Responses for the T-Anxiety scale assess frequency of feelings “in general”: 1) almost never, 2) sometimes, 3) often, and 4) almost always [11].

4) **BDI-II (Beck Depression Inventory –II):** is a self-administered questionnaire for the dimensional evaluation of depressive symptoms. Twenty-one symptoms of depression are rated on a 4-point scale 0, within the time frame of the past two weeks. Each question includes

four statements graded by intensity of depressive symptoms. The subject must respond based on the answer that best describes his state of mind on a scale ranging from 0 to 3. The individual scores are then added up into a total score which is interpreted as follows: 0-13 = normal performance; 13-29 = mild to moderate depression; 30-36 = severe depression [12].

5) **SF-36 (Short-Form 36 Item):** generic tool for assessing quality of life in samples of the general population, widely used also in samples of patients with psychiatric disorders; it produces a score for each item, that are physical functioning, role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; emotional well-being, social functioning, pain, general health and health change. Higher scores correspond to greater well-being [13].

6) **STAXI – 2:** a 57-item questionnaire that includes six scales, five subscales, and an overall measurement of total anger expression. The state anger scale (RS scale) assesses the intensity of anger as an emotional state at a particular time. It has three subscales: feeling angry (RS.S), feel like expressing anger verbally (RS.V), and feel like expressing anger physically (RS.F). The trait anger scale (RT scale) assesses how often angry feelings are experienced over time. It has two subscales: angry temperament (RT.T), which measures the disposition to experience anger without provocation, and angry reaction (RT.R), which measures how frequently angry feelings are experienced in situations that involve frustration or negative evaluations. The anger expression in scale (ER IN) assesses how angry feelings are checked or suppressed. The anger expression out scale (ER OUT) measures the expression of angry feelings toward other persons or objects in the environment. The anger control in scale (CR IN) assesses how people control angry feelings by calming down or cooling off and the anger control out scale (CR OUT) assesses how people control angry feelings by preventing the expression of anger toward other persons or objects in the environment. Matching the results of anger expression out, anger expression in, and anger control in scales, a general index of the expression of anger, indicated by ER Index, is obtained. Raw scores on STAXI-2 scales

are converted into sex- and age-specific T-scores, normalized by comparing them with an Italian control group matched for age and sex. T-scores above 75 were considered outside the normative range and thus were used to identify an uncontrolled level of anger [14, 15].

RESULTS

We enrolled 53 patients (57.9 ± 13.5 years old), 24 male (45.3%) and 29 female. Thirty-four patients were affected by acromegaly (ACRO), while 19 had a non-functioning pituitary adenoma (NFPA). All the subjects in ACRO group had IGF-I levels < ULN for age and IGF-I/ULN median 0.6 (0.4; 0.8) as for inclusion criteria (Table 1). In ACRO group we also distinguished *cured* ACRO (n. 8) and *controlled* ACRO (n. 26) as defined in "methods paragraph". All main clinical features are summarized in Table 1. All the 53 patients completed questionnaires, while only 45 patients (ACRO n. 27; NFA n. 18) underwent M.I.N.I. interview. The main reasons patients did not accepted the interview were: 1) lack of time (n. 3); 2) belief of not having psychological problems (n. 3) and 3) negative opinions about psychological care (n. 2). All NFPA subjects had a macroadenoma (mean diameter 25.3 ± 9.1 mm), while in ACRO group four subjects had a microadenoma, 28 a macroadenoma (mean diameter 19.5 ± 12.1 mm, p 0.07) and two patients had not detectable pituitary lesions. We recorded a significantly difference between ACRO and NFPA for gender (p 0.025), treatment with radiotherapy (p 0.010) and hypocortisolism (p 0.0001). Moreover the number of visits in the last years was significantly higher in ACRO group (p 0.0001). Instead, no differences in age at enrolment, neurosurgery treatment, number of prescribed medications, hypothyroidism, hypogonadism diagnosis and duration of follow up were detected.

We also analysed differences between *controlled* and *cured* ACRO (Table 2). The two groups proved to be different for age at enrolment (p 0.039), neurosurgery performed (p 0.013) and radiotherapy treatment (p 0.009), IGF-I/ULN ratio (p 0.047) and prolactin levels at the enrolment (p 0.039) as well as number of visits in the last year (p 0.0001). No difference was detected in duration of follow up and duration of controlled disease.

QUESTIONNAIRES SCORES RESULTS

STAI questionnaire (Table 1S and 2S in supplemental materials)

No difference was detected in trait anxiety between ACRO and NFPA, (p 0.08); however, the NFPA showed a trend toward greater state of anxiety compared to ACRO. No differences were found between *controlled* and *cured* ACRO, between NFPA and *controlled* or *cured* ACRO.

BDI questionnaire (Table 1S and 2S in supplemental materials)

35.3% of ACRO patients (n.12) showed a pathological BDI score compared to 21.1% of NFPA patients (n.4) (p 0.202). GH, IGF-I, prolactin and testosterone levels at the enrolment did not correlate to BDI score.

SF-36 Questionnaire (Table 1S and 2S in supplemental materials)

ACRO obtained a significant lower score in "emotional well-being" items (p 0.008) and, even if not significant, in "energy/fatigue" items (p 0.088) vs NFPA. The difference in well-being remained significant even in univariate and multivariate regression (table 3). The same difference (p 0.023) was found if we consider only *controlled* ACRO, and even in this case acromegaly remained strongly associated in multivariate regression (adjusted for age, duration of follow up and hypocortisolism); the number of visits in the last year proved to be the stronger negative factor (p 0.044; r -0.31). No significant difference was found between *controlled* and *cured* ACRO, even if the formers obtained a better score in "Health change" items (p 0.061). The most significant differences were highlighted between NFPA and *cured* ACRO. In fact NFPA patients obtained higher scores in "emotional well-being", "energy/fatigue" and "general health" items (respectively p 0.032; 0.007; 0.015) compared with *cured* ACRO. However only "emotional well-being" and "general health" scores proved to be negatively associated to *cured* acromegaly in multivariate regression (analysis adjusted for gender, age, hypocortisolism and number of visits). Table 4. Also in this case, GH, IGF-I, prolactin and testosterone levels at the enrolment did not correlate to SF-36 scores.

STAXI-2 Questionnaire (Table 1S and 2S in supplemental materials)

RS.F score (expression of anger physically) proved to be significantly higher in ACRO (p 0.004) compared to NFPA; on the contrary ACRO patients obtained a lower score (p 0.027) in CR.IN (how people control angry feelings). These differences were confirmed also at univariate and multivariate regression analysis (adjusted for gender, age, duration of disease and testosterone levels, Table 5). In particular, the difference in RS.F score was also found comparing NFPA with *controlled* ACRO (p 0.004) and between NFPA and *cured* ACRO (p 0.06), even if in the latter case the significance was lost. Similarly CR.IN difference was detected also between NFPA and *cured* ACRO (p 0.005), but not between NFPA and *controlled* ACRO.

PASQ and ACRO quality of Life Questionnaire (Table 3S in supplemental materials)

PASQ and ACROQoL questionnaires were administrated only to patients with acromegaly. No differences were detected between *controlled* and *cured* ACRO groups.

M.I.N.I. Interview

Forty-five patients (ACRO 27 and NFPA 18) agreed to undergo the M.I.N.I interview. Nineteen (42.2 %) subjects had a pathological result, while 26 proved not to have a psychiatric disorder. In particular no difference was detected between ACRO and NFPA for psychiatric disorders, even if a higher rate of pathological results was found in acromegaly patients (51.8% vs 27.7%). In ACRO, nine patients suffered for anxiety, while five had a major depressive episode; in NFPA two subjects had anxiety disorders and three a major depressive episode. Finally, no difference was found between *controlled* and *cured* ACRO or NFPA and *cured* or *controlled* ACRO. Figure 1.

DISCUSSION

The present study showed a higher rate of unknown psychiatric disorders in patients suffering from acromegaly compared to subjects affected by non-functioning pituitary adenoma, despite normal

IGF-I or remission of the disease. Although not statistically significant, probably due to the small sample size, this difference confirmed Literature data that identify acromegaly as a disease with a greater risk of developing affective disorders, particularly depression, compared to patients with other chronic diseases [5]. As previously described by Pernichetti in a recent review [16] acromegaly subjects mostly experience anxiety and depression, while schizophrenia and manic-depressive psychoses are relatively rare occurrences. In our study anxiety and depression were the most representative psychiatric diseases. In particular, several patients have suffered for a major depression episode, that it was not reported by patient in his medical history. However, we did not find worsen scores in the specific questionnaires for depression (BDI) and anxiety (STAI), both in *controlled* and *cured* acromegalic patients, compared to NFPA patients. In this regard, surprisingly also specific questionnaires for acromegaly diseases did not show differences between *controlled* and *cured* patients. In fact no differences were found in PASQ and AcroQoL scores in these two groups, prompting to think that not the actual disease control, but rather the memory of the previous GH hypersecretion could be the main factor for the development of symptoms and quality of life disturbances. To support this, we did not find any correlation between PASQ and AcroQoL scores and GH or IGF-I levels at the enrolment. However, available data are conflicting about this. Previous studies demonstrated that adding GH receptor agonist to somatostatin receptor ligands (SRL) in already well controlled acromegaly patients improves quality of life and PASQ score suggesting that normal IGF-I levels is not enough to normalize QoL [17]. Moreover it has been documented that patients with cured acromegaly did not obtain better cognitive measures than untreated patients, and rather the length of disease or remission were related to neurocognitive state, suggesting that effects of chronic exposure to GH/IGF-I hypersecretion might have long-term effects on brain functions [18]. Analysing SF-36 questionnaire results, we detected a lower score in the "emotional well-being" items in acromegaly group, but if we consider only *cured* subject this difference becomes more evident. Cured patients had a worse perception about their current healthy state in comparison to patients with *controlled* acromegaly [19]. In fact, interestingly, *cured* patients seem to feel worsen compared to

controlled patients in "emotional well-being", in "energy/fatigue" and in general health" items. An interesting explanation could be that recovered patients may feel abandoned by their doctors; in fact subjects under treatment are usually regularly monitored and periodically in contact with their doctors, more than *cured* one. In fact, in our population the number of visits requested in the last year for *cured* subjects was statistically lower compared to *controlled* ones. However to date, no data are available on this regard. Another possible interpretation could be a sort of relative growth hormone deficiency in *cured* acromegaly patients compared to *controlled* ones. In fact, an increased prevalence of psychiatric disorders and poor QoL have been reported in patients with adult GH deficiency [20]. In our Centre, GH deficiency is not routinely screened in cured acromegaly patients; however in the study no significant difference was detected at the enrolment in IGF-I or GH levels between patients with *controlled* disease under therapy and cured disease at the enrolment.

In some studies, female gender, macroadenomas, and history of radiotherapy (RT) are associated with worse psychological status, including mainly depression, anxiety, fatigue, and confusion [21]. In our study male gender, (but not RT and adenoma diameter) demonstrated to be positively associated to well-being (p 0.027) and energy (p 0.035). However, in multivariate regression we confirmed that gender and RT did not influence none of our previous results, underlining, as acromegaly was the stronger predictor.

As anger is a possible expression of depressive symptoms, another aim of our study was to evaluate anger feelings in acromegaly population. Our findings demonstrated that controlled acromegaly subjects were not angrier than NFPA patients, nor than general population. In fact none of patients totalized a pathological score in STAXI questionnaire. Suppression and expression of angry emotion have been associated with a wide range of health complications, including cardiovascular disease [22], respiratory illness, musculoskeletal problems, and pain disorders [23]. Although acromegaly is characterized by all these complications, we have not found an increased angry feeling in our acromegalic population. However, we noticed some significant differences between ACRO and

NFPA groups. In fact in acromegaly patients the ability to control anger (CR.IN) is lower and the physical expression of it (RS.F) higher than NFPA suggesting a more aggressive behaviour. None of these differences was associated to testosterone levels or hypogonadism status.

We can't exclude that adjuvant medical treatment of acromegaly may have a role in the pathogenesis of psychiatric alterations. Dopamine agonists (DA) are known to be associated with a higher incidence of impulse control diseases (ICDs) while SRL and GH receptor antagonist appears to have no role in psychiatric diseases pathogenesis. Considering all population, patients taking DA seemed to obtain a worst score in SF36-well being item (p 0.054 – result not shown). Despite this, analysing the possible interference of DA treatment, only in *controlled* ACRO group, DA therapy was not associated with a better or worse questionnaire score. However, it cannot be excluded that these results are due to the small sample size.

CONCLUSION

In conclusion, this study highlighted how psychiatric disease seems to be more represented in patients suffering from acromegaly (despite normal IGF-I levels) compared to NFPA. Recovery from the disease, does not necessarily improve QoL scores, in fact in cured patients the quality of life can be even worse, as detected in our study. Hence, it is mandatory to support patient suffering from acromegaly, even if definitively cured, and to investigate psychiatric disorders and give psychological support during medical treatment.

Author contribution: all authors contributed to the study conception and design, in particular CC, UA and GM for the psychiatric aspects. Material preparation, data collection and analysis were performed by NP, CC, GM, FB and AB. SG, CB, VG, EV and DC enrolled patients. All authors read and approved the final manuscript.

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FIGURES

Figure 1. Comparison of M.I.N.I interview results between acromegalic patients (cured and controlled) and patients suffering from non-functioning adenoma

TABLES

Table 1. Main clinical features of all study population, ACRO group and NFPA group

VARIABLE	Tot (n. 53)	ACRO (n. 34)	NFPA (n. 19)	p value
Age at enrolment (mean ± SD)	57.9 ± 13.5	55.7 ± 14.2	61.9 ± 11.6	0.111
Sex; male (%)	24 (45.3)	11 (32.3)	13 (68.4)	**0.025**
Micro/Macro/No pituitary lesion	4/47/2	4/28/2	0/19/0	0.539
Adenoma diameter mm (mean ± SD)	21.6 ± 11.4	19.5 ± 12.1	25.3 ± 9.1	0.077
Neurosurgery n (%)	37 (69.8)	21 (61.8)	16 (84.2)	0.163
Radiotherapy n (%)	4 (7.5)	3 (8.8)	1 (5.3)	**0.010**
Hypothyroidism n (%)	19 (35.8)	10 (29.4)	9 (47.4)	0.313
Secondary Hypogonadism n (%))	11 (20.8)	5 (14.7)	6 (31.6)	0.206
Menopause n (%)	18 (62)	14 (60.9)	4 (21.1)	NA
Hypocortisolism	19 (35.8)	5 (14.7)	14 (73.7)	**0.0001**
GH deficiency	5 (9.4)	NA	5 (26.3)	NA
Diabetes insipidus	2 (3.8)	0 (0)	2 (10.5)	0.239
Testosteron levels (male) ng/ml mean ± SD	4.4 ± 1.8	3.8 ± 2.9	4.6 ± 1.1	0.609
IGF-I median (IQR) ng/ml		167 (120;230)*		
IGF-I/ULN median (IQR)		0.6 (0.4; 0.8)*		
GH median (IQR) ng/ml		1.2 (0.4 - 2.3)*		
Prolactin median (IQR) ng/ml		10.6 (0.9 - 25.3)*		
Acromegaly treatment (monotherapy or combined) Somatostatin receptor ligands Pegvisomant Cabergoline		26/34 17 3 8		
Duration of follow up (years) median (IQR)	7 (2.7;13)	8.5 (1;13)	5 (4;12.3)	0.738
Number of visits in last year median (IQR)	4 (2;12)	12 (4;12)	3 (2;4)	**0.0001**
Number of prescribed medications median (IQR)	4 (1;7)	5 (2;8)	3 (1;6)	0.177

Abbreviation: ACRO, acromegaly; NFPA, non-functioning pituitary adenoma; GH, growth hormone; IGF-I, insulin like growth factor I; SD, standard deviation; ULN, upper limit normal; IQR, interquartile range; *available only in acromegaly patients at the enrolment; *in bold p<0.05*

Table 2. Differences in main features between Controlled vs Cured ACRO

VARIABLE	Controlled ACRO (n. 26)	Cured ACRO (n. 8)	p value
Age (mean ± SD)	58.5 ± 14.6	46.7 ± 8.3	**0.039**
Sex; male (%)	7 (26.9%)	4 (50%)	0.388
Micro/Macro/No pituitary lesion at the enrolment	4/20/2	0/0/8	0.468
Adenoma diameter mm at diagnosis (mean ± SD)	18 ± 12.8	24.2 ± 8.6	0.219
Neurosurgery n (%)	13 (50%)	8 (100)	**0.013**
Radiotherapy n (%)	0 (0)	3 (37.5)	**0.009**
Hypothyroidism n (%)	7 (26.9)	3 (37.5)	0.666
Secondary Hypogonadism n (%))	3 (11.5)	2 (25)	0.986
Menopause n (%)	14 (53.8)	0 (0)	**0.029**
Hypocortisolism	4 (15.4)	1 (12.5)	1.000
Growth hormone deficiency	NA	NA	NA
Diabetes insipidus	0	0	NA
Testosteron levels (male) ng/ml	4.2 ± 4.1	3.3 ± 0.9	0.502
IGF-I median (IQR) ng/ml	169 (127;230)	149 (119; 197)	0.516
IGF-I/ULN median (IQR)	0.6 (0.5; 0.9)	0.4 (0.4; 0.6)	**0.047**
GH median (IQR) ng/ml	1.25 (0.6; 2.2)	0.5 (0.1; 2.9)	0.228
Prolactin median (IQR) ng/ml	5.6 (0.3; 17.4)	19 (12.7; 37.2)	**0.039**
Duration of follow up (years) median (IQR)	9.5 (3;14)	4 (1;11)	0.254
Duration of controlled disease (years) median (IQR)	7 (4; 10)	3 (1; 8.5)	0.169
Number of visits in last year median (IQR)	12 (10;12)	3 (2;4)	**0.0001**
Number of prescribed medications median (IQR)	6 (4;8)	2 (0;5)	0.060

Abbreviation: NFPA, non-functioning pituitary adenoma; ACRO, acromegaly; SD, standard deviation; GH, growth hormone; IGF-I, insulin like growth factor I; ULN, upper limit normal; IQR, interquartile range; NA, not applicable; *in bold p<0.05*

Table 3. Multivariate regression between ACRO and NFPA for SF-36 WELL-BEING

Model 1	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-10.2924	5.1241	-0.2785	-2.009	**0.05**
Sex	6.5795	4.9211	0.1895	1,337	0.1875
Model 2	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-12.2678	4.8418	-0.3435	-2.534	**0.0146**
Age	0.1389	0.1712	0.1163	0,811	0.4213
Model 3	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-13.4615	4.7461	-0.3789	-2.836	**0.0067**
Year of follow-up	0.3217	0.3223	0.1426	0,998	0.3233
Model 4	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-11.822	5.8701	-0.2791	-2.014	**0.0496**
Number of visits	-0.2254	0.6277	-0.05177	-0.359	0.7211
Model 5	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-23,2017	6,1460	-0,5551	-3,775	0,0007
Hypocortisolism	-8,4076	6,5281	-0,2220	-1,288	0,2070
Model 6	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-21,5427	5,7911	-0,5378	-3,720	0,0007
Radiotherapy	0,1727	8,5242	0,003475	0,0203	0,9840

Table 4. Multivariate regression between Cured ACRO and NFPA for SF-36 WELL-BEING (A) and SF-36 GENERAL HEALTH (B)

A) WELL-BEING

Model 1	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-9.5545	3.4777	-0.4971	-2.747	**0.0115**
Gender	3.0099	6.7478	0.09261	0.446	0.6597
model 2	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-9.2347	4.0629	-0.4283	-2.273	**0.0327**
Age	0.08771	0.2974	0.06139	0.295	0.7707
Model 3	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-13.6904	3.834	-0.5972	-3.571	**0.0016**
Hypocortisolism	-12.7307	7.0991	-0.3502	-1.793	0.0861
Model 4	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-10.2923	3.1242	-0.5662	-3.294	**0.0032**
Number of visits	-4.1496	1.9537	-0.4049	-2.124	**0,0446**
Model 5	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-11.0345	3.6908	-0.529	-2.99	**0.0065**
Radiotherapy	7.1724	9.4427	0.1564	0.76	0,4552

B) GENERAL HEALTH

Model 1	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-11.3274	3.8913	-0.5189	-2.911	**0.0079**
Gender	-1.6337	7.5502	-0.04507	-0.216	0.8306
Model 2	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-13.1783	4.4728	-0.5235	-2.946	**0.0072**
Age	-0.2725	0.3274	-0.171	-0.832	0.4137
Model 3	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-16.8731	4.0217	-0.6584	-4.196	**0.0003**
Hypocortisolism	-19.1796	7.4467	-0.4731	-2.576	0.0169
Model 4	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-11.5585	3.5381	-0.563	-3.267	**0.0034**
Number of visits	-4.2446	2.2125	-0.3714	-1.918	0.0675
Model 5	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-7.1921	3.6466	-0.3803	-1.972	**0.0607**
Radiotherapy	-24.7537	9.3295	-0.4841	-2.653	0.0142

Table 5. Multivariate regression between ACRO and NFPA for STAXI-2 RS.F and STAXI-2 CR IN scores.

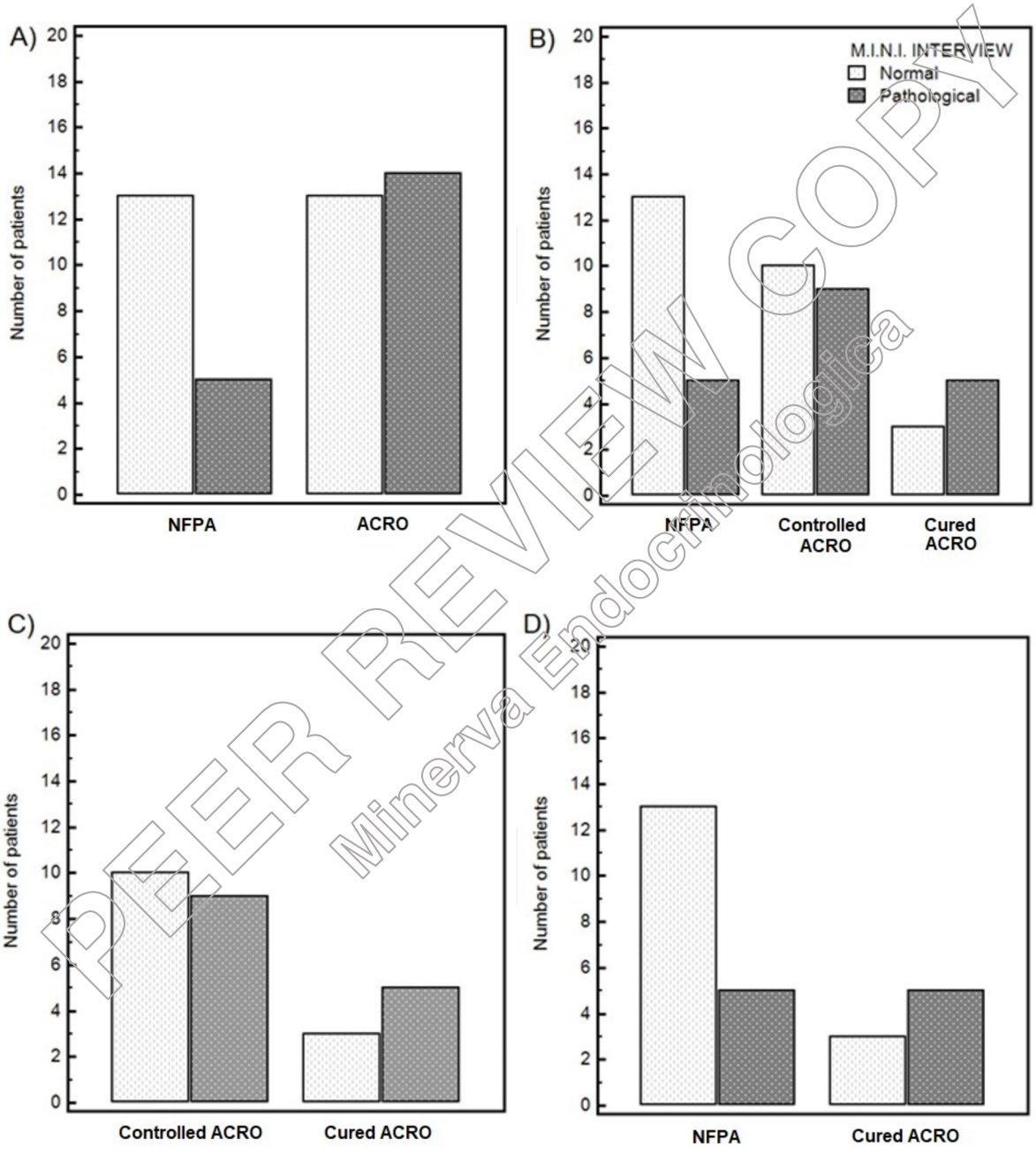
A) STAXI-2_RS.F

Model 1	Coefficient	Std. Error	rpartial	t	P
Acromegaly	1.2231	0.4902	0.3388	2.495	**0.0161**
Gender	-0.9911	0.6764	-0.2069	-1.465	0.1493
Model 2	Coefficient	Std. Error	rpartial	t	P
Acromegaly	1.0886	0.5094	0.2948	2.137	**0.0377**
Age	-0.04291	0.02695	-0.224	-1.592	0.1179
Model 3	Coefficient	Std. Error	rpartial	t	P
Acromegaly	2.2592	0.9394	0.5407	2.405	**0.0306**
Testosterone levels	0.0002366	0.003796	0.01666	0.0623	0.9512
Model 4	Coefficient	Std. Error	rpartial	t	P
Acromegaly	1.9434	0.7355	0.5087	2.642	**0.0156**
Years of follow up	0.003053	0.09873	0.006914	0.0309	0.9756

B) STAXI-2_CR IN

Model 1	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-7,0473	1,8515	-0,4777	-3,806	**0.0004**
Gender	-4,5979	2,5366	-0,2507	-1,813	0.076
Model 2	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-5,386	1,9276	-0,3707	-2,794	**0.0074**
Age	0,1559	0,09835	0,2209	1,585	0.1193
Model 3	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-5,9982	4,4263	-0,3405	-1,355	0.1968
Testosterone levels	-0,006919	0,01789	-0,1028	-0,387	0.7047
Model 4	Coefficient	Std. Error	rpartial	t	P
Acromegaly	-6,2985	1,8349	-0,4403	-3,433	**0.0012**
Years of follow up	0,2525	0,1758	0,2009	1,436	0.1574

Abbreviation: ACRO, acromegaly; NFPA, non-functioning pituitary adenoma; RS.F, expressing anger physically score; CR IN, anger control in scale score



Supplementary Digital Material

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