Mental health in patients with adrenal incidentalomas: is there a relation with different degrees of cortisol secretion?

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Abstract

Context. Cushing's syndrome frequently causes mental health impairment. Data in patients with adrenal incidentaloma (AI) are lacking.

Objective. We aimed to evaluate psychiatric and neurocognitive functions in AI patients, in relation to the presence of subclinical hypercortisolism (SH), and the effect of adrenalectomy on mental health.

Design. We enrolled 62 AI patients (64.8±8.9 yrs) referred to our Centers. SH was diagnosed when cortisol after 1mg-dexamethasone suppression test was >50 nmol/L, in the absence of signs of overt hypercortisolism, in 43 patients (SH+).

Interventions. The Structured Clinical Interview for DSM-5 and 5 Psychiatric Scales were performed. The Brief Assessment of Cognition in Schizophrenia (Verbal and Working Memory, Token and Symbol Task, Verbal Fluency, Tower of London) was explored in 26 patients (≤65 yrs).

Results. The prevalence of psychiatric disorders was 27.4% (SH+ 30.2% *vs* SH- 21.1%, p=0.45). SH+ showed a higher prevalence of middle insomnia (by Hamilton Depression Rating Scale) compared to SH- (51% *vs* 22%, p=0.039). Considering Sheehan Disability

Scale, SH+ showed higher disability score (7 *vs* 3, p=0.019), higher perceived stress (4.2±1.9 *vs* 2.9±1.9, p=0.015) and lower perceived social support (75 *vs* 80, p=0.036) than SH-. A high perceived stress was independently associated with SH (OR=5.46, CI95% 1.4-21.8, p=0.016). Interestingly, SH+ performed better in verbal fluency (49.5±38.9 *vs* 38.9±9.0, p=0.012), symbol coding (54.1±6.7 *vs* 42.3±15.5, p=0.013) and Tower of London (15.1 *vs* 10.9, p=0.009) than SH-. In 8 operated SH+ no significant changes were found.

Conclusions. SH may influence patients' mental health and cognitive performances requiring an integrate treatment.

Keywords: subclinical hypercortisolism, adrenal incidentaloma, mental health, cognition

Introduction

Glucocorticoids, mainly cortisol, play a crucial role in the allostatic process of adjustment to stressors and can determine important changes in central nervous system structures (1-3). It is well known that overt endogenous hypercortisolism is associated with psychiatric and neurocognitive impairment in about two thirds of cases. The most important psychiatric disorders observed in Cushing's syndrome (CS) are major depression, including disturbance of appetite or sleep, mania and anxiety. Concerning cognitive functions, in CS the most frequent reported alterations are memory impairment (about 83% of cases) and reduced concentration (66% of cases) (4). Unfortunately, these alterations are only partially reversible after the hypercortisolism resolution (5-6).

Although clinically silent, at least 20% of patients with incidentally found adrenal adenomas (adrenal incidentaloma, AI) may present with a mild hypercortisolism, less severe than CS, formerly called subclinical hypercortisolism (SH) or autonomous cortisol secretion (7). Though cardiovascular and bone consequences of these clinically silent adrenal masses have been largely explored and documented, data related to the impact of SH on mental health are scarce and, as regard as cognitive function, absent (8-9).

In the present study we firstly aimed to explore mental health and cognitive functions in AI patients in relation to the presence of SH and, secondly, in a group of SH+ patients, the effect of adrenalectomy on mental health.

Patients

In this Italian multicenter study, we prospectively evaluated 470 consecutive patients with AI referred to the Endocrinology Unit of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and the Endocrinology and Diabetology Service of IRCCS Istituto Ortopedico Galeazzi in Milan, and the Endocrinology Unit of Fondazione IRCCS Casa

Sollievo della Sofferenza, in San Giovanni Rotondo, Foggia, from April 2016 to May 2019. The following exclusion criteria were applied: active malignancies, bilateral micro- or macro-nodular adrenal hyperplasia, maximum diameter of AI ≤1 cm, primary hyperaldosteronism, pheochromocytoma, suspected adrenocortical carcinoma or adrenal metastases, adrenal pseudocysts or myelolipomas, ACTH-dependent hypercortisolism, presence of signs or symptoms of overt hypercortisolism, steroid or gonadal therapy or other drugs interfering with cortisol determination after dexamethasone suppression test. Patients satisfying the inclusion criteria (n=154) were asked to take part to the study: 62 (40.3%) patients accepted and were enrolled (Figure 1); among these, 28 were also enrolled in an interventional randomized trial supported by Italian Ministry of Health (RF 2013-02356606 grant). Written informed consent was obtained from all subjects, and the local Ethics Committees approved the study. Patients were divided in two groups: patients with subclinical hypercortisolism (SH+), if in the presence of serum cortisol after 1mg dexamethasone overnight suppression test (1mgDST) >50 nmol/L (i.e., with at least possible autonomous cortisol secretion according to the ESE-ENSAT guidelines) and patients without SH (SH-) in the presence of serum cortisol levels after 1mgDST ≤50 nmol/L (10). In a sub-analysis we performed a comparison of some cognitive variables among three groups (1-2-3), divided according to cortisol levels after 1mgDST (<50, 50-138 and <138 nmol/L, respectively).

Methods

All patients were evaluated by measuring: 1) plasma ACTH levels at 8 am (Immulite 2000, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA); 2) 24-hours urinary free cortisol (UFC) by LC–MS/MS as previously described (11); 3) serum cortisol levels after 1mgDST (Roche II, Elecsys Cortisol immunoassay, Roche Diagnostics, Mannheim, Germany on CobaS E 602) in at least two occasions. the latest available measurement was reported in

the statistical analysis. In all patients height and weight were measured and body mass index (BMI) calculated.

Data regarding diameter of the AI in the latest performed computed tomography scan and assumption of psychotropic drugs were also collected.

Psychiatric evaluation

Trained psychiatrists, blinded to the hormonal profile, assessed all patients. Included subjects were firstly screened by SCID-5 (Structured Clinical Interview for DSM-5), a semi-structured interview for the DSM-5 psychiatric diagnoses (Diagnostic and Statistical Manual of Mental Disorders -5) (12). Global Severity of psychiatric symptoms were then assessed by CGIs (Clinical Global Impression – Severity of Illness) scale (13), patients' functioning by GAF (Global Assessement of Functioning) scale (14), severity of main psychiatric symptoms by BPRS (Brief Psychiatric Rating Scale) (15), severity of depressive symptoms by HAM-D (Hamilton Depression Rating Scale) (16) and severity of manic symptoms by YMRS (Young Mania Rating Scale) (17). Psychiatrists evaluated sleep disturbances by sleep diminution item of YMRS scale (YMRSi) and initial (HAM1i), middle (HAM2i) and late insomnia (HAM3i) items of HAM-D scale. Unfortunately, scores of these latter items were unavailable for 5 patients. We considered the subjects as affected by sleep disorders in case of HAM1i, HAM2i, HAM3i or YMRSi scores $\geq$1 (16-17). In addition, the Sheehan Disability Scale (SDS) (18) was used to measure the severity of dysfunction in work, social life/leisure activities, family life/home responsibilities (SDS-Disability), as well as the perceived levels of stress (SDS-Stress) and social support (defined as percentage of the social support thought necessary for an adequate functioning- SDS-Social support).

Eight out of 28 patients, who were enrolled for the interventional randomized trial, were re-evaluated after surgery in terms of mental health, 3 months after the interruption of steroid replacement therapy.

Cognitive evaluation

Cognitive evaluation could be assessed only in 26 patients, aged ≤65 years. The choice to test cognition only in patients younger than 65 years was based on the high frequency of cognitive decline (e.g. mild cognitive impairment) in elderly subjects independently from the presence of SH. Included subjects were evaluated by a clinical psychologist by the Italian version of BACS (Brief Assessment Cognition in Schizophrenia). BACS is a reliable tool to assess cognition in healthy subjects and in patients affected by psychiatric disorders (19-21). This battery includes tests to assess verbal memory (by list learning task), working memory (by digit sequencing task), motor speed (by token motor task), verbal fluency (by category instances and controlled oral words association test), attention and speed information processing (by symbol coding task), executive functions (by Tower of London task). Data were expressed as corrected scores, adjusted for age, gender and education where relevant, according to the multiple regression model used in the validation study of the Italian version of BACS (20).

Statistical analysis

We performed statistical analysis by using SPSS version 25.0 statistical package software (SPSS Inc, Chicago, Illinois). For each variable normality of distribution was tested by Shapiro-Wilk test. Quantitative variables were expressed as mean±SD and range or median and interquartile range when not normally distributed. The SH+ and SH- groups were compared by independent sample t-tests or Mann-Whitney U tests, as appropriate. Qualitative variables were expressed as absolute number count (percentage) and compared by chi-

squared tests or Fisher's exact tests, as appropriate. Bivariate associations among variables were tested by Pearson product moment (r) or Spearman's rank correlation (r_s), as appropriate. A logistic regression assessed the association between high levels of SDS-Disability, high levels of SDS-Stress and low levels of SDS-Social support (dependent variables) and the SH presence and possible confounding factors when appropriate (age, gender, and BMI). The comparison of quantitative variables among the three groups (1-2-3), divided according to cortisol levels after 1mgDST (<50, 50-138 and <138 nmol/L, respectively), was performed by one-way-ANOVAs. Data of 8 SH patients before surgery and 3 months after stopping steroid replacement therapy were compared by paired sample t-tests. Two-tailed p values <0.05 were considered as statistically significant.

Results

Clinical and hormonal variables of the whole cohort of SH+ and SH- group are shown in Table 1. The 64.5% of patients were females, mainly distributed in SH+ group. The two groups were comparable for age, BMI, consumption of psychotropic drugs, while female gender was prevalent in SH+ group. All female patients, except 3 reporting regular menses, were in menopause. Among male patients, none complained symptoms or presented signs related to hypogonadism. As expected, in SH+ group, we found lower plasma ACTH levels, higher cortisol levels after 1mgDST and a larger diameter of the adenoma when compared with the SH- group, though the UFC levels were similar in both groups. In 5 subjects the UFC concentrations were above the upper limit of normal reference range but in the absence of clinical stigmata of CS.

Psychiatric interview (SCID-5)

In 17 out of 62 patients (27.4%) a psychiatric disorder was diagnosed by the SCID-5 interview: 13 SH+ and 4 SH- (30.2% vs. 21.1% in SH+ and SH- groups, respectively p=0.45). Specifically, 11 patients were diagnosed with Generalized Anxiety Disorder – GAD: 9 from the SH+ and 2 from the SH- (21% *vs* 10.5% respectively; p=0.32). Among the non-GAD SH+ patients, 2 patients were diagnosed with bipolar disorder (versus 0 in SH- group), 1 patient with cyclothymic disorder, 1 patient with unspecified depressive disorder. Among the non-GAD SH- patients, we observed 1 patient with major depressive disorder and 1 patient with panic disorder. Differently from SH+ group, in SH- group patients diagnosed with a psychiatric disorder showed higher UFC levels (p=0.025) compared to SH- patients without a psychiatric condition, while no differences in ACTH levels or cortisol after 1mgDST were observed (data not shown). Among the 5 patients with UFC > ULN, 2 were diagnosed with GAD (one belonging to the SH+ group and one belonging to SH- group).

Psychiatric rating scales

The median scores derived from the psychiatric scales HAM-D, BPRS, YMRS and CGIs did not significantly differ between SH+ and SH-groups. With regard to SDS item mean total scores, SH+ patients were found to have higher levels of disability related to mental illness (SDS-Disability), higher levels of perceived stress (SDS-Stress) and lower levels of perceived social support (SDS-Social support) as compared with SH- patients (Table 2). The logistic regression analysis showed that high levels of SDS-Disability (≥4 in a scale of 30) were significantly associated with the SH+ condition (OR=5.5, CI 95% 1.5-20.4, p=0.01) regardless of age (OR=0.97, CI 95% 0.9-1.0, p=0.493), gender (OR=1.39, CI 95% 0.4-4.9, p=0.606) and BMI (OR=1.0, CI 95% 0.9-1.1, p=0.926). Similarly, high levels of SDS-Stress (≥4 in a scale of 10) were significantly associated with the SH+ condition (OR=5.9, CI 95% 1.4-22.8, p=0.015), but not with female gender (OR=1.6, CI 95% 0.5-5.8,

p=0.44), BMI (OR=1.09, CI 95% 1-1.2, p=0.18) nor with age (OR=0.97, CI 95% 0.9-1.0, p=0.51). Moreover, low levels of SDS-Social support (<70 in a scale of 100) were associated with the presence of SH+ condition (OR=3.7, CI 95% 1.0-14, p=0.05) but not with age (OR=1.0, CI 95% 0.9-1.0, p=0.744) nor with gender (OR=1.8, CI 95% 0.5-6.3, p=0.345). Considering hormonal and psychiatric variables, UFC levels showed a direct correlation with BPRS total scores (rs=0.35, p=0.005) and ACTH levels were inversely correlated with SDS-disability scores (rs=-0.28, p=0.029). Analyzing specific items included in HAM-D and YMRS sleep scales, we observed a higher frequency of middle insomnia (HAM2i) in SH+ compared to SH- patients (Table 3). There was also a trend towards an increased prevalence of sleep diminution (YMRSi) in SH+ compared to SH- group (p=0.1). Considering hormonal and psychiatric variables, UFC levels showed a weak direct correlation with the scores of sleep reduction – YMRSi (rs=0.27, p=0.042).

Cognitive evaluation (BACS)

BACS cognitive evaluation was conducted only in patients aged ≤65 years. We did not observe any statistically significant difference between SH+ and SH- patients regarding verbal memory as well as working memory neither in absolute numbers nor as percentage of cases with impaired cognition. Interestingly, SH+ patients performed better in verbal fluency, symbol coding and Tower of London as absolute scores than SH- ones. Moreover, with regard to symbol coding and Tower of London tasks we observed a higher frequency of impaired cognition in SH- subjects than in SH+ ones (Table 4).

Among cognitive variables, verbal fluency was positively correlated with symbol coding (r_s= 0.78, p<0.001) and Tower of London (rs=0.39, p=0.049). With regard to functional parameters, UFC levels were directly correlated with performances in symbol coding task (rs=0.50, p=0.009), but inversely with the verbal memory ones (rs=-0.43, p=0.027); cortisol levels after 1mgDST were directly correlated with performances in Tower of London task

(rs=0.40, p=0.043). Moreover, diameter of AI was directly correlated with performances in verbal fluency (rs=0.58, p=0.002) and symbol coding task (rs=0.67, p <0.001). To better explore this association we further divided SH+ patients into 2 groups according to cortisol levels after 1mgDST, thus obtaining 3 groups of patients: those with cortisol ≤50 nmol/L (group 1corresponding to SH-, without autonomous cortisol hypersecretion, n=10), those with cortisol between 50-138 nmol/L (group 2, with possible autonomous cortisol secretion, n=13) and those with cortisol greater than 138 nmol/L (group 3, with autonomous cortisol hypersecretion, n=3) (10). With regard to the Tower of London task mean scores, we found that patients of group 2 performed better than patients in both groups 1 and 3 (Figure 2).

Surgical outcome

All the SH+ patients who underwent adrenalectomy (n=8) received glucocorticoid replacement therapy for at least 1 month after surgery. Then, in the presence of adrenal insufficiency, HPA-axis function was re-evaluated every 3 months by Synacthen test. The mean duration of glucocorticoid replacement therapy was 9.3±6.2 months (range 1-19). Parameters of adrenal function and psychiatric evaluations were reassessed 3 months after the interruption of steroid replacement therapy.

Comparing basal with post-surgical parameters, we observed a significant increase in mean ACTH levels (1.9±0.5 pmol/L vs 6.3±4.2 pmol/L, p=0.02, respectively), a reduction of cortisol levels after 1mgDST (91.1±35.9 nmol/L vs 27.0±11.3 nmol/L, p=0.017, respectively) and a reduction of UFC levels, even though without reaching statistical significance (78.1±71.2 nmol/24h vs 37.5±26.9 nmol/24h, p=0.227). The 2 patients with a psychiatric diagnosis at baseline (1 cyclothymia and 1 GAD) maintained their diagnosis after surgery. Overall, we did not find any significant improvement in any psychiatric scores. However, the

SDS-Disability score tended to improve, but without achieving statistical significance (8.1±4.6 *vs* 4.9±4.6, p=0.140, before and after surgery, respectively); similarly, after surgery, we found a negative correlation between variation of ACTH levels and variation of SDS-Disability levels (r=-0.60, p=0.12), although without reaching the statistical significance.

Discussion

This is the first study that explores in AI patients the effects of clinically silent hypercortisolism and adrenalectomy on mental health by the use of a comprehensive battery of psychiatric rating scales and cognitive tests.

Our results did not show a higher prevalence of psychiatric disorders in SH+ patients compared with SH- ones. However, in SH+ group we observed increased levels of disability related to mental illness, higher levels of perceived stress, lower levels of perceived social support and higher prevalence of middle insomnia than in SH- one. Interestingly, SH+ patients showed better cognitive functions in specific items, namely verbal fluency, attention and information processing and executive planning functions, than SH- ones. Finally, in SH+ group, 3 patients showed bipolar spectrum disorders that are known to be associated with an increased activity of hypothalamus-pituitary-adrenal axis (22). Overall, these findings are of clinical interest since in the general population the prevalence of the adrenal adenoma and SH are elevated, reaching the 4-9% and 0.2-2%, respectively (23). Therefore, our results confirm and reinforce the idea that even a low degree of cortisol excess may be deleterious for psychological health. Indeed, in the past years, a study performed by generic questionnaires suggested a reduction of health-related quality of life (QoL) in AI patients; however, the role of the degree of cortisol excess has not been elucidated (24). Subsequently, the possibility of a QoL improvement after adrenalectomy in SH patients has been reported (25), suggesting

that the QoL impairment could be a further consequence of SH. The present results clearly show that patients with SH have a reduction of psychological health and QoL.

The possible causative role of a low degree of cortisol excess on psychiatric and neurocognitive impairment is explainable considering that cortisol plays a crucial role in the allostatic process of adjustment to stressors and can determine important changes in central nervous system structures. Likewise, CS is associated with psychiatric and neurocognitive impairment in the majority of patients (2-4), with these alterations being only partially reversible with the hypercortisolism resolution (5-6). One of the most important psychiatric disorders observed in CS is major depression, including disturbance of appetite or sleep (4). Although we did not find a high prevalence of major depression in SH+ group, these patients presented with a higher prevalence of middle insomnia, resembling the feature detected in CS patients (26-27). The sleep reduction has a pivotal role in determining the quality of life and increasing data show that poor quality of sleep may increase the risk of cardiovascular diseases (28). We speculate that sleep disturbances may be caused by even mild degree of hypercortisolism, while major depression is mainly related to overt cortisol excess. Of note, sleep disturbances often represent the first sign of the onset of a depressive episode and in any case, they represent a risk factor for future of depression (29). In support of this hypothesis, the occurrence of major depression in CS is mainly related to elevated UFC levels, which are generally in the normal range in patients with SH (30). The prevalence of anxiety disorders, detected in the 21% of SH+ patients, is higher than the 5% reported in the general population. The anxiety disorders' prevalence remains higher than expected although in our cohort of SH+ patients we have a large representation of female subjects, in whom the risk of GAD is doubled (31). Interestingly, we found 3 GAD and 1 major depression cases among SH- patients, characterized by UFC levels higher than those observed in patients without psychiatric disorders, further suggesting the close relationship between psychiatric

health and the degree of cortisol secretion, even in patients considered without SH. This is in agreement with recent data suggesting that some chronic metabolic disorders, such as hypertension, diabetes and osteoporosis may be related to the cortisol secretion, sensitivity and peripheral activity even in subjects without adrenal adenoma or hypercortisolism (32-33).

The evidence of an impact of the SH condition on QoL in the present study is furthermore confirmed by the finding that SH+ patients had higher levels of SDS-Disability, higher levels of SDS-Stress and lower levels of SDS-Social support as compared with SH- patients. In particular, perceived stress, that could be expected to be higher in women, was independent of gender, age and BMI, possible confounding factors. Similarly, low levels of SDS-Social support were associated with SH regardless of age. Unfortunately, we do not have data about the socioeconomic status. However, the relation between socioeconomic status and psychological health can be considered bidirectional. Indeed, a low socioeconomic status could be considered the cause as well as the result of a psychiatric disturbance. Even though we cannot provide a clear-cut idea on the surgical outcome of these patients, in the light of the small sample size and the short follow-up, the finding that the SDS-Disability score slightly improves after surgery suggests a reversibility of the perceived stress in SH patients. However, in the absence of a control group and a longer follow-up, it is not possible to exclude that, as in CS patients, the impairment of QoL could persist lifelong (34).

Differently from most CS patients experiencing memory impairment and reduced concentration (4), these alterations were not found in SH+ patients. Nonetheless, SH+ patients performed better in verbal fluency, information processing speed (symbol coding task) and executive planning functions (Tower of London task) than SH- ones. The differences detected between SH+ and SH- patients could be explained if considering that symbol coding, verbal fluency and Tower of London require the activation of the pre-frontal cortex (35-37), whose performance are demonstrated to be improved by little amount of

exogenous steroids (38). The finding that, in Tower of London task, patients with an intermediate degree of cortisol secretion (i.e. those with cortisol after 1mgDST between 50 and 138 nmol/L) performed better than patients with a higher degree of cortisol secretion (i.e. those with cortisol after 1mgDST above 138 nmol/L) and without SH (Figure 2) is in keeping with the idea that a little amount of cortisol hypersecretion may improve these cognitive functions. The association of the degree of cortisol secretion with features of cognitive functions mimics the inverted U adaptive stress response (2), in which intermediate cortisol levels are associated to a positive hyperactivity of central nervous system, while a further increase of the cortisol levels is associated with a maladaptive response. To confirm this hypothesis and to elucidate the reasons why our findings in cognitive tasks were quite the opposite of those described in CS, we would need a larger sample of patients, possibly including subjects with overt hypercortisolism.

We are aware that the present study suffers from some limitations. Firstly, the sample size of patient who underwent cognitive function evaluation was limited. However, we are confident that our results are informative, as this item has never been evaluated so far and, importantly, at variance with previous studies (24, 39), our cases were diagnosed by psychiatrist and not by generic self-administered quality of life questionnaires, thus increasing the diagnostic accuracy. Secondly, we have a higher prevalence of SH+ (69%) than SH- patients, probably due to a greater concern of SH+ patients about their health. This apparently high prevalence of SH+ patients is in agreement with the use, for the SH diagnosis, of a cut-off for cortisol after 1mgDST set at 50 nmol/L. Indeed, by using this cut-off the prevalence of this condition may exceed 40% of AI patients (40). Moreover, we recognize that a recruiter bias might be present, as well: between 2016 and 2019 due to the randomized trial supported by Italian Ministry of Health (RF 2013-02356606 grant), specifically designed to evaluate effects of surgery in SH+ patients, conducted in the 3

centers involved in this study, a high number of SH+ patients, larger than usual, has been evaluated, specifically sent by other centers. A third limitation of the study is the absence of a real control group of healthy subjects. Indeed, the inclusion of a control group of subjects without AI could have been more informative on the possibility that, even in AI patients without SH diagnosis, the degree of cortisol secretion could in fact impact on QoL, as suggested for other complications of cortisol excess, such as hypertension, diabetes and osteoporosis (32-33). Lastly, the lack of correlation between cortisol levels and different analysed items suggests that the cortisol secretion might not entirely explain the QoL impairment in SH. Therefore, data regarding the individual sensitivity to glucocorticoids (e.g. GC receptor polymorphisms and 11β-hydroxysteroid dehydrogenase activity) or the androgens levels could have been useful, considering the potential role of these specific factors in neuropsychiatric illness (41-43). Certainly, our study does not demonstrate causality but only associations. The only findings supportive of possible causality are the suppressed baseline ACTH levels that increase after surgery and the inverse correlation of ACTH levels with SDS disability scores. It is however important to notice that the presence of low ACTH levels, permits to differentiate a SH sustained by an adrenal adenoma, from a pseudo-Cushing's syndrome, recently referred to as physiologic/ non-neoplastic hypercortisolism (44). Indeed, pseudo-Cushing's syndrome is characterized by an increase in HPA axis activity and a meta-analyses showed higher ACTH levels in both bipolar and depressed individuals compared to healthy subjects (22, 45). Therefore, in our opinion, our exclusion criterion of ACTH-dependent hypercortisolism should have made it unlikely to have enrolled "pseudo-Cushing patients" in SH+ group. Regarding to the psychiatric features of an "ACTH-independent subclinical hypercortisolism" we could expect them to be rather similar to those of "pseudo-Cushing patients", as no differences between pituitary-dependent and independent CS were described (46).

In conclusion, besides the metabolic complications, mental health should be evaluated in AI patients. Indeed, SH may be associated to increased levels of disability related to mental illness, higher levels of perceived stress, lower levels of perceived social support and higher prevalence of middle insomnia. On the other hand, the presence of slight cortisol excess may be associated with a better performance in some cognitive functions. These data could be useful for ameliorating our protocols for the diagnostic work-up, addressing the treatment of choice and setting-up rehabilitative procedures in patients with AI.

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Data Availability: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Legend to fig.1

Enrolled patients after application of exclusion criteria

Legend to fig.2

Tower of London task mean scores in 3 groups of patients according to cortisol levels after 1mgDST: in deep grey patients with cortisol ≤50 nmol/L; in black with cortisol between 50-138 nmol/L and in light gray with cortisol greater than 138 nmol/L.

Table 1. Clinical and hormonal variables in the whole sample of patients and divided into SH+ and SH- groups

Variables	All patients (n=62)	SH+ Group (n=43)	SH- Group (n=19)	*p*
Age, y mean ± SD (range)	64.8 ±8.9 (30-79)	64.5 ±9.4 (30-76)	65.3 ±7.8 (51-79)	NS
Women, n (%)	40 (64.5)	32 (74.4)	8 (42.1)	0.014
Patients taking psychopharmacotherapy n (%)	13 (21.0)	10 (23.3)	3 (15.8)	NS
BMI, kg/m^2 mean ± SD (range)	26.7± 4.6 (18.5-35.4)	26.6 ±4.7 (18.5-35.2)	27.1 ±4.4 (20.7-35.4)	NS
Diameter of AI, cm mean ± SD (range)	2.8 ±0.9 (1.1-5.3)	3.0 ±0.9 (1.5-5.3)	2.4 ±0.9 (1.1-5.0)	0.018
ACTH (pmol/L) median (interquartile range)	2.3 (2)	1.9 (1.1)	4.2 (1.9)	<0.001
1mgDST (nmol/L) median (interquartile range)	66.2 (64.3)	88.3 (55.2)	34.2 (13.8)	<0.001
UFC (nmol/24h) median (interquartile range)	51.4 (46.6)	50.8 (48.6)	52.8 (42.2)	NS
UFC >ULN, n (%)	5 (8.1)	4 (9.3)	1 (5.6)	NS

Data are expressed as mean values ±SD (range), or median (interquartile range) or absolute numbers, n and percentage in brackets (%).

BMI, Body Mass Index; 1mg DST, serum cortisol after 1mg dexamethasone overnight suppression test; UFC, 24-hour Urinary Free Cortisol; UFC >ULN, UFC> upper limit of reference range.

p values referred to the comparisons between SH+ and SH- groups, *p* values < 0.05 were considered as statistically significant, NS: not significant *p* value.

Table 2. Psychiatric rating scale scores and percentage of subjects with clinically significant psychiatric symptoms in SH+ and SH- group.

	SH+ (n=43)	SH- (n=19)	*p*
Depression - HAMD (0-34) median (interquartile range)	5 (3)	5 (4)	NS
Clinically significant HAM-D (>7), n (%)	*9 (20.9)*	*3 (15.8)*	NS
Brief Psychiatric Rating - BPRS (0-126) median (interquartile range)	23 (5)	23 (4)	NS
Clinically significant BPRS (≥31), n (%)	*1 (2.3)*	*0 (0)*	NS
Mania – YMRS (0-36) median (interquartile range)	4 (3)	4 (6)	NS
Clinically significant YMRS (≥10), n (%)	*3 (7)*	*0 (0)*	NS
Impression of severity – CGI-S (1-7) median (interquartile range)	1 (1)	1 (0)	NS
Clinically significant CGIs (>1) n (%)	*16 (37.2)*	*4 (21.1)*	NS
Functioning - GAF (0-100) mean ± SD (range)	82.7 ± 6.1 (68-92)	82.5 ±7.9 (63-94)	NS
SDS - Disability (0-30) median (interquartile range)	7 (7)	3 (6)	0.019
SDS - Stress (0-10) mean ± SD (range)	4.2 ±1.9 (0-8)	2.9 ±1.9 (0-7)	0.015

SDS – Social Support (0-100) median (interquartile range)	75 (40)	80 (30)	0.036

In the left column for each scale, theoretical extremes, if available, are reported in brackets. Quantitative variables are expressed as mean±SD (range) or median (interquartile range) when non-normally distributed. For HAMD, BPRS, YMRS and CGI-S scales, number of patients with scores beyond the threshold conventionally considered as clinically relevant and percentage (in brackets) are also reported in italics. *p* values < 0.05 were considered as statistically significant, NS: not significant *p* value.

Table 3. Patients with sleep disorders

	SH+ (n=39)	SH- (n=18)	*p*
Presence of HAM1i (%)	10 (25.6)	6 (33.3)	NS
Presence of HAM2i (%)	20 (51.3)	4 (22.2)	0.039
Presence of HAM3i (%)	12 (30.8)	4 (22.2)	NS
Presence of YMRSi (%)	22 (56.4)	6 (33.3)	NS

Initial (HAM1i), central (HAM2i) and late (HAM3i) insomnia of HAM-D scale; YMRSi= sleep diminution item of YMRS scale. We considered the presence of HAM1i, HAM2i, HAM3i and YMRSi for scores ≥1 for each item. Data are expressed as absolute numbers and percentages in brackets.

Table 4. *Cognitive evaluation by BACS in SH+ and SH- patients*

	SH+ (n=16)	SH- (n=10)	*p*
Verbal memory mean ± SD (range)	48.8 ±10.7 (21.5-65.5)	52.0 ±7.8 (38.5-64.3)	NS
Impaired verbal memory (<33), n (%)	1 (6.3)	0 (0)	NS
Working memory median (interquartile range)	21.8 (8.6)	23.9 (18.4)	NS
Impaired working memory (<14.9), n (%)	3 (18.8)	1 (10)	NS
Token task mean ± SD (range)	67.7 ±8.6 (49.5-83.5)	70.6±10.3 (54.75-85.7)	NS
Impaired token task (<68.7), n (%)	11 (68.8)	5 (50)	NS
Verbal fluency mean ± SD (range)	49.5 ±38.9 (31.5-72.2)	38.92 ±9 (26.75-58.5)	0.012
Impaired verbal fluency (<31.6), n (%)	1 (6.3)	2 (20)	NS
Symbol coding mean ± SD (range)	54.1 ±6.7 (38.5-63.3)	42.27 ±15.5 (7.75-59.5)	0.013
Impaired symbol coding (<40.5), n (%)	1 (6.3)	4 (40)	0.055
Tower of London median (interquartile range)	15.1 (4.1)	10.9 (3.6)	0.009
Impaired Tower of London (<12.4), n (%)	2 (12.5)	6 (60)	0.026

Quantitative variables are expressed as mean±SD (range) or median (interquartile range) if non-normally distributed. Number of cases with impaired performance and percentages in brackets are also reported for each task. The cut-offs for cognitive deficits are defined in the validation study of the Italian version of BACS (20).

Figure -1

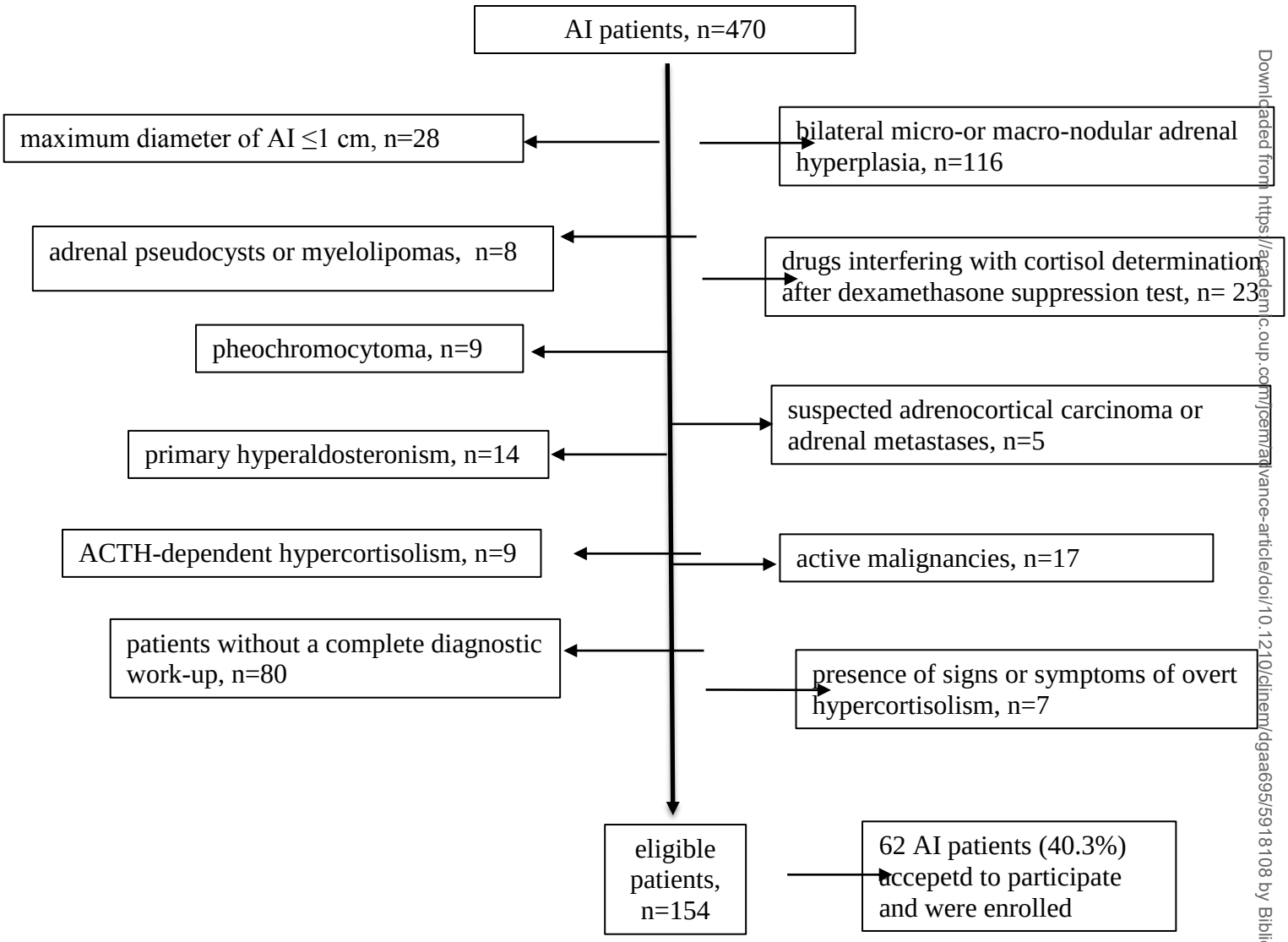

Figure -2