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Coping strategies in patients after treatment for functioning or nonfunctioning pituitary adenomas



Abstract

Context and objective: Coping strategies may affect quality of life (QoL), which is decreased in patients after treatment for Cushing's disease, acromegaly, or nonfunctioning pituitary macroadenomas (NFMA). We aimed to explore coping strategies in these patients because this has never been done before.

Design: This was a cross-sectional study.

Subjects: We included patients treated for Cushing's disease (n=42), for acromegaly (n=80), and for NFMA (n=61). These patients were compared with three reference populations: an a-select sample from the Dutch population (n=712), patients with chronic pain (n=59), and patients receiving primary care psychology services (n=525). Furthermore, the three patient groups were compared with each other. Coping strategies were assessed by the Utrecht Coping List.

Results: Compared with the a-select sample, patients with pituitary adenomas reported less active coping (P<0.0001), sought less social support (P<0.0001), and reported more avoidant coping (P=0.008). In contrast, patients treated for pituitary adenomas reported somewhat better coping strategies than patients with chronic pain and those with psychological disease. When patients with different pituitary adenomas were compared, patients treated for Cushing's disease sought more social support than patients treated for NFMA (P=0.035).

Conclusions: Patients treated for pituitary adenomas display different and less effective coping strategies compared with healthy controls. A targeted intervention might help to stimulate patients to use a more active coping strategy and to seek social support, instead of an avoiding coping strategy. This might, in turn, improve their QoL.

Introduction

Pituitary adenomas may result in considerable, chronic comorbidity. Hormone overproduction results in classical syndromes like Cushing's disease and acromegaly. Mass effects of the tumor, especially in non-functioning pituitary macroadenoma (NFMA) result in visual field defects and hypopituitarism. Transsphenoidal surgery is an effective therapy for control of tumor mass and hormone overproduction in the majority of patients. If necessary, additional treatment with medical treatment or incidentally radiotherapy is available. Patients treated for Cushing's disease, acromegaly, and NFMA have persistently impaired quality of life (QoL) despite long-term cure (1-3). The factors causing reduced QoL in those patients with pituitary adenomas have not been fully elucidated. Coping is the way in which someone reacts (behaviorally, cognitively, and emotionally) to situations that require adjustments in dealing with an adverse event and/or its consequences, for example an illness and its treatment (4). The common sense model (CSM) of illness cognition conceptualizes the processes involved in the adaption to threats imposed by illness. According to this CSM, coping strategies are determinants of medical outcomes (5). Furthermore, it is thought that coping may affect QoL (6).

At present, there are no studies that report coping strategies in patients with treated Cushing's disease, acromegaly or NFMA. Therefore, we aimed to examine the coping strategies of patients after treatment for pituitary adenomas in comparison with reference groups.

Patients and Methods

Design

We conducted a cross-sectional study in which patients treated for pituitary adenomas were invited to fill out a questionnaire on coping strategies.

Inclusion criteria were age over 18yr and treatment for pituitary adenoma at least 1yr ago. The protocol was approved by the institutional Medical Ethics Committee.

Patients

Patients with treated pituitary adenomas were invited to participate in the current study. These patients suffered from Cushing's disease, acromegaly, or NFMA. Patients were asked to complete a questionnaire on coping strategies at home and re-

turn this questionnaire in a prepaid envelope. Overall, the clinical characteristics of the non-participants did not differ from those of the participants.

Cushing's disease: A clinical chart review of 51 patients who had been treated by transsphenoidal surgery, if necessary followed by repeated surgery and/or post-operative radiotherapy was performed. We selected these patients based on their participation in an earlier study on psychopathology and personality traits (7). Nine patients (18%) refused to participate for several reasons including old age, and/or debilitating disease. Forty-two patients (82%) participated in the current study and completed the questionnaire.

Acromegaly: A clinical chart review of 156 patients who had been treated for acromegaly was performed. Fifty six patients (36%) refused to participate and an additional 20 patients (13%) did not (completely) fill out the measure used to assess coping (see below). Eighty patients (51%) participated in the current study and completed all questionnaires.

NFMA: A clinical chart review of 100 patients treated for NFMA was performed. Twenty five patients (25%) refused to participate and 14 patients (14%) did not (completely) fill out the measure used to assess coping (see below). Sixty one patients (61%) participated in the current study and completed all questionnaires.

Treatment and follow-up

Cushing's disease

Cushing's disease had been diagnosed based on internationally agreed guidelines, i.e. the clinical manifestations and positive biochemical tests including increased urinary excretion rates of free cortisol, decreased overnight suppression by dexamethasone (1mg) and, since 2004, elevated midnight salivary cortisol values, in addition to non-suppressed ACTH levels. All patients had been treated by transsphenoidal surgery, if necessary followed by repeated surgery and/or post-operative radiotherapy. Cure of Cushing's disease was defined by normal overnight suppression of plasma cortisol levels (<50nmol/l) after administration of dexamethasone (1mg) and normal 24h urinary excretion rates of cortisol (<220nmol/24h). Hydrocortisone independency was defined as a normal cortisol response to CRH or insulin-tolerance test (ITT). At the time of the current study, all patients were in remission of Cushing's disease.

Acromegaly

The diagnosis of acromegaly had been established by clinical signs and symptoms and by biochemical tests, including insufficient suppression of GH during glucose tolerance test and increased IGF-1 levels for age. Cure of acromegaly was defined by normal serum IGF-1 levels for age and serum GH levels below $1.9\mu g/l$ for all

patients and, in patients without somatostatin analogue treatment, also by normal suppression of GH levels (<0.38 mcg/l) during glucose tolerance test (8). Remission was confirmed by repeating the tests at yearly intervals. At the time of the current study, all patients were in remission or biochemically controlled. The biochemically controlled patients all had a IGF-I concentration in the normal range for age.

Non-functioning pituitary adenomas

After surgical treatment for NFMA, which was histopathologically confirmed, NFMA patients were included. Surgical treatment was performed in case of visual field defects in the majority of patients. Postoperatively, MRI scans were performed to detect tumor recurrence or regrowth. In case of progression, patients were referred for radiotherapy or an expectative management was chosen. At the time of the current study, all patients were free of recurrence of NFMA.

Follow-up

Patients were followed at our outpatient department. Patients were monitored for (recurrence of) disease, according to appropriate dynamic tests in patients with functioning adenoma and MRI scans in patients with non-functioning adenoma. In all patients, pituitary function was monitored and pituitary hormone replacement was prescribed dependent on the results of the yearly evaluation of pituitary functions. In case of corticotrope insufficiency, confirmed by insulin-tolerance test or CRH test, the average dose of hydrocortisone was 20mg/d divided into 2 to 3 dosages. Evaluation of GH deficiency was performed by insulin-tolerance test and/or GHRH-arginine test, only in patients under the age of 70yr and only after at least 2yr of remission. Somatotrope insufficiency was treated with recombinant human GH replacement, aiming at a IGF-I concentration in the normal range for age. In acromegaly, patients were treated with GH from 2005 onwards during a controlled trial of recombinant human GH replacement (9). In addition, free T₄ and testosterone levels (in male patients) were assessed. If results were below the lower limit of the respective reference ranges, substitution with L- T_{Δ} and/or testosterone was prescribed. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided.

Utrecht Coping List (UCL)

The UCL is an established Dutch coping scale with well-documented reliability and validity (10). Although its validity has not been tested for pituitary patients, the scores on the UCL in various medical samples have been reported in the international medical literature (6;11-13). The UCL consists of 47 statements where

the patients indicate whether they find these applicable to themselves. A four-point scale was used, ranging from seldom or never to very often. The statements lead to seven subscales: active coping (score ranging from 7-28), seeking distraction (score ranging from 8-32), avoiding (score ranging from 8-32), seeking social support (score ranging from 6-24), passive coping (score ranging from 7-28), expressing emotions (score ranging from 3-12), and fostering reassuring thoughts (score ranging from 5-20).

The subscale active coping refers to the ability to disentangle the situation and purposefully working to solve the problem. Seeking distraction refers to seeking distraction not to have to think regarding the problem and trying to feel better by smoking, drinking, or relaxation. Avoiding refers to leaving the problem for what it is or running away from it. Seeking social support refers to seeking social support for comfort and understanding or asking for help. Passive coping refers to being completely overwhelmed by the problem, a negative view and worrying about the past. Expressing emotions refers to the ability to show irritation or anger. Fostering reassuring thoughts refers to optimism (4).

Dutch population norms are available for nurses and women from the general population aged 18-65 years (4), as well as for chronic pain patients (10), and patients receiving primary care psychology services (14).

Reference populations

The a-select sample consisted of 712 women from two groups; the first group consisted of nurses with a mean age 30yr, while the second group was a random selection from the Dutch population with a mean age 47yr (4;14).

The chronic pain reference group consisted of 59 Dutch patients. This sample consists of 44 women and 15 men with a mean age of 64±6yr. Patients who reported pain in the hip or knee in the last month on three separate occasions during the study were classified as chronic pain patients.

The group of patients receiving primary care psychology services consisted of 525 Dutch patients who were in psychotherapy during the time of study. The group incorporated 329 women and 196 men, with a mean age of 37 ± 12 yr. Most patients were referred to a primary care psychologist by their general practitioner (37%) or self-referral (23%). All patients suffered from DSM-IV Axis-1 diagnosis, and an additional 68% also suffered from a DSM-IV Axis-2 personality disorder (14).

Statistical analysis

Data were analyzed using PASW Statistics version 17.0.2 (SPSS Inc., Chicago, IL, USA). All data were presented as mean \pm standard deviations, unless mentioned otherwise. The primary analysis comprised the comparison of the results in pa-

tients who were treated for pituitary adenoma and of results in various reference groups. Means were calculated for all subscales of the UCL and compared between groups using Student's t-test. The level of significance for this analysis was set at $P \le 0.01$, because multiple comparisons were performed. The secondary analysis comprised the comparison of results between patients treated for Cushing's disease, patients treated for acromegaly, and patients treated for NFMA. A general linear model was used to compare the UCL scores, with surgery, postoperative additional radiotherapy, and hypopituitarism as fixed factors. A *post hoc* analysis with a Bonferroni correction was performed in case of significant differences. The level of significance for this analysis was set at $P \le 0.05$.

Results

Sociodemographic and clinical characteristics

Patients after treatment for Cushing's disease

Clinical characteristics of the patients are detailed in Table 1. All patients with Cushing's disease had been treated by transsphenoidal surgery, and nine patients (21%) had received additional radiotherapy because of persistent disease after surgery. At the time of the current study, all patients were in remission, with a mean duration of follow-up after cure of 13±10yr, and 27 patients (64%) were treated for some degree of pituitary insufficiency.

Patients after treatment of acromegaly

The clinical characteristics of patients after treatment for acromegaly are detailed in Table 1. Most of the patients (84%) had been treated by transsphenoidal surgery and 18 patients (23%) had been treated by additional radiotherapy because of persistent disease after surgery. Twenty eight patients (35%) were treated by somatostatin analogs, nine patients (10%) received pegvisomant therapy, and six patients (8%) received dopamine-agonist therapy. All patients were in remission or biochemically controlled at the time of study. The mean duration of follow-up was 16±10yr. At the time of the current study, 30 patients (38%) required treatment for pituitary insufficiency. Since not all patients were surgically cured, possible differences between surgically cured patients, patients receiving surgery and additional radiotherapy, and patients receiving chronic injections were analyzed using a one-way ANOVA with a *post hoc* Bonferroni correction. However, there were no significant differences in coping strategies between these groups.

Patients after treatment of NFMA

The clinical characteristics of patients after treatment for NFMA are detailed in Table 1. All patients had been treated by transsphenoidal surgery and 28 patients (46%) underwent additional radiotherapy because of persistent disease after surgery. At the time of the current study, all patients were free of recurrence of NFMA, with a mean duration of follow-up of 16 ± 10 yr, and all patients were treated for some degree of pituitary insufficiency.

Table 1 Clinical characteristics

	Cushing's disease (n=42)	Acromegaly (n=80)	NFMA (n=61)
Gender (male/female)	6/36	45/35	31/30
Age in years	54 (12)	60 (12)	63 (12)
Education (n)	Low: 19	Low: 23	Low: 12
	Medium: 11	Medium: 26	Medium: 24
	High: 12	High: 31	High: 25
Transsphenoidal surgery (%)	42 (100%)	67 (84%)	61 (100%)
Additional radiotherapy (%)	9 (21%)	18 (23%)	28 (46%)
Somatostatin analogue therapy, n (%)	NA	28 (35%)	NA
Pegvisomant therapy, n (%)	NA	9 (10%)	NA
Dopa agonist therapy, n (%)	NA	6 (8%)	NA
Duration of follow-up (yrs)	13 (10)	16 (10)	16 (10)
Hypopituitarism (%)	Any axis: 27 (64%)	Any axis: 30 (38%)	Any axis: 61 (100%)
	GH: 19 (45%)	GH: 12 (15%)	GH: 46 (75%)
	LH/FSH: 12 (29%)	LH/FSH: 15 (19%)	LH/FSH: 54 (89%)
	TSH: 17 (41%)	TSH: 21 (26%)	TSH: 46 (75%)
	ACTH: 24 (57%)	ACTH: 21 (26%)	ACTH: 47 (77%)

Data are mean (SD) unless otherwise stated; NA, not applicable

Coping strategies in patients after treatment for pituitary adenomas

Coping strategies in patients after treatment for pituitary adenomas compared with an a-select sample from the Dutch population

Patients treated for pituitary adenomas had significantly lower scores on active coping and seeking social support, and higher scores on the avoiding scale compared with an a-select sample from the Dutch population.

A lower score on active coping (P<0.0001) indicates that patients with pituitary adenomas performed worse when it came to disentangling the situation and purposefully working to solve the problem. A lower score on seeking social support (P<0.0001) suggests that patients with pituitary adenomas sought less comfort and understanding from others and therefore probably received less social support. The higher score on avoiding (P=0.008) indicates that they left the problem to what is was or ran away from it.

Figure 1 shows the scores of the patients with treated pituitary disease and the reference groups on the UCL, whereas Figure 2 shows how many patients scored in the most maladaptive percentile: 95th or higher percentile for avoiding and passive

Distribution of scores of patients treated pituitary adenomas and the reference groups

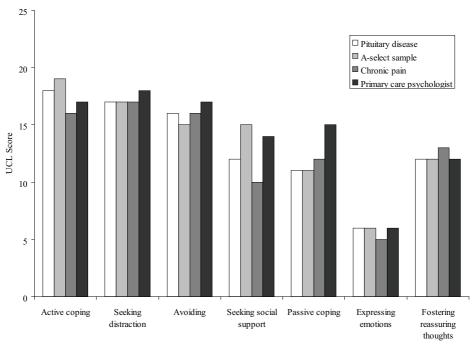


Figure 1: Distribution of scores of patients with long-term cure of pituitary adenomas and the reference groups. Means are displayed in this figure. The coping strategies Avoiding and Passive coping are negative strategies, which means that a higher score indicates a more maladaptive coping strategy. The coping strategies Active coping, Seeking distraction, Seeking social support, Expressing emotions, and Fostering reassuring thoughts are positive strategies, which means that lower scores indicate a more maladaptive coping strategy.

coping, and 5th or lower percentile for active coping, seeking distraction, seeking social support, expressing emotions, and fostering reassuring thoughts (4).

Coping strategies in patients after treatment for pituitary adenomas compared with other diseases

Coping strategies of patients with pituitary adenomas were compared with patients who suffered from chronic pain. The latter patient group reported pain in the hip or knee in the last month on three separate occasions. Compared with these patients, patients with treated pituitary adenomas scored higher on seeking social support (P<0.0001), indicating that patients with treated pituitary adenomas sought more comfort and understanding from others and therefore probably received more social support.

Coping strategies of patients with pituitary adenomas were also compared with the group of patients receiving primary care psychology services. All patients suffered

Distribution of UCL scores in the most maladaptive (<5th or >95th) percentile of patients with treated Cushing's disease, acromegaly, or NFMA

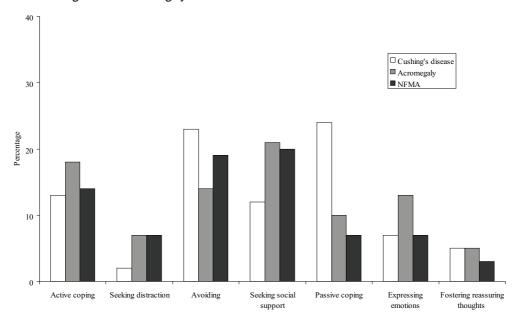


Figure 2: Distribution of how many patients scored in the most maladaptive percentile based on the scores of an a-select sample from the Dutch population. \geq 95th percentile for Avoiding and Passive coping, \leq 5th percentile for Active coping, Seeking distraction, Seeking social support, Expressing emotions, and Fostering reassuring thoughts were used. Percentages are displayed in this figure.

from a DSM-IV Axis-1 diagnosis, and an additional 68% also suffered from a DSM-IV Axis-2 personality disorder. Patients with pituitary adenomas scored lower on avoiding, seeking social support, passive coping, and expressing emotions.

A lower score on the coping strategy avoiding (P<0.0001) indicates that patients with pituitary adenomas were less intended to leave the problem to what it was. Lower scores on seeking social support (P<0.0001) suggest that patients with pituitary adenomas sought less comfort and understanding from others and therefore probably received less social support. Furthermore, a lower score on passive coping (P<0.0001) suggests that these patients were less overwhelmed by the problem. A lower score on expressing emotions (P<0.0001) suggests that patients with pituitary adenomas were less able to show irritation or anger compared with patients in primary care psychology services.

Patients with pituitary adenomas scored higher on active coping (P=0.0005) compared with patients receiving primary care psychology services, which indicates that patients with pituitary adenomas work better at disentangling the situation and purposefully working to solve the problem.

15.3 (4)**

6.3 (2)**

11.6(3)

Passive coping

thoughts

Expressing emotions

Fostering reassuring

UCL	Pituitary patients, n=183	A-select sample, n=712	Chronic Pain, n=59	Patients in primary care psychology services, n=525
Active coping	17.6 (4)	19 (5)**	16.4 (4)	16.5 (4)**
Seeking distraction	17.1 (4)	17 (6)	16.8 (4)	17.7 (4)
Avoiding	15.9 (3)	15 (6)*	16.0 (3)	17.1 (4)**
Seeking social support	12.2 (4)	15 (5)**	10.2 (3)**	13.5 (4)**

11 (5)

6(2)

12 (4)

11.7 (4)

5.3(2)

13.3 (3)

Table 2 Comparison of pituitary patients' UCL scores with other populations

11.0 (3)

5.7 (2)

12.1 (3)

Data are mean (SD), * p<0.01 compared with pituitary patients, ** p<0.001 compared with pituitary patients

Comparison of coping strategies in patients with Cushing's disease, acromegaly, and NFMA

Because sociodemographic characteristics do not influence coping strategies (14), we corrected only for surgery, additional radiotherapy, and hypopituitarism in comparing the patient groups. When the patient groups were compared, just one significant difference was found in coping strategies. When performing a *post hoc* analysis, patients with NFMA appeared to seek less social support compared with patients with Cushing's disease (P=0.035).

In addition, possible differences between short-term (<10yr) and long-term follow-up (\geq 10yr) in these pituitary patients were analyzed, correcting for diagnosis (i.e. Cushing's disease, acromegaly, or NFMA). In the short term follow-up group, there were 67 (27 males) patients (age 56 ± 13 yr) *versus* 116 (56 males) patients (age 61 ± 12 yr) in the long-term follow-up group. There was no significant difference in gender distribution. Age, however, differed between these two groups, with the long-term follow-up group being slightly older. Nonetheless, there were no significant differences in coping between these two groups. This suggests that the duration of follow-up does not influence coping strategies.

Furthermore, patients who had been treated by transsphenoidal surgery were compared with patients who had been treated by transsphenoidal surgery and additional radiotherapy, correcting for diagnosis (i.e. Cushing's disease, acromegaly, or NFMA). The group of patients who had been treated by surgery consisted of 116 subjects (52 males, age 58±13yr), and the group of patients receiving surgery and radiotherapy consisted of 54 subjects (23 males, age 63±12yr). Thirteen patients (all with acromegaly) were excluded from this comparison, since they had

not been treated by surgery. There were no significant differences in coping strategies between patients treated by surgery only and by both surgery and radiotherapy. This indicates that the addition of radiotherapy does not influence coping strategies in our cohort of patients.

Lastly, we also compared coping strategies between patients with hypopituitarism (i.e. insufficiency of at least one pituitary axis) and without hypopituitarism, correcting for diagnosis (i.e. Cushing's disease, acromegaly, or NFMA). There were 118 patients (52 males, age 58±13yr) with hypopituitarism and 65 patients (31 males, age 60±12yr) without hypopituitarism. There were no significant differences in coping strategies between these patient groups. This indicates that hypopituitarism also does not affect coping strategies.

Table 3 Comparison of pituitary patients

	Cushing's	Acromegaly	NFMA	P-value
UCL	disease	(n=80)	(n=61)	
	(n=42)			
Active coping	17.5 (3)	17.4 (4)	18.0 (3)	0.727
Seeking distraction	17.7 (3)	16.9 (4)	17.1 (4)	0.896
Avoiding	16.3 (3)	15.5 (4)	16.2 (3.1)	0.546
Seeking social support	13.3 (4)	12.1 (4)	11.4(3)	0.016*
Passive coping	12.0(3)	10.5 (3)	10.8 (3)	0.730
Expressing emotions	5.9(2)	5.6 (2)	5.7(2)	0.760
Fostering reassuring	12.3 (3)	12.1 (3)	12.1 (3)	0.664
thoughts				

Data are mean (SD), * Post Hoc Bonferroni analysis revealed a significant difference between Cushing's disease and NFMA (p=0.035)

Discussion

This explorative study demonstrates that patients after treatment for pituitary adenomas report less active coping and more avoidance coping and seek less social support compared with an a-select sample from the Dutch population. Compared with patients with chronic pain, patients treated for pituitary adenomas sought more social support. Patients after treatment for pituitary disease were also compared with patients in primary care psychology services. Patients with pituitary adenomas scored lower on avoiding, seeking social support, passive coping, and expressing emotions, but higher on active coping. This indicates that patients treated for pituitary adenomas report less effective coping strategies compared with the normal population, but apparently use more effective coping strategies than patients with chronic pain and patients in primary care psychology services. Furthermore, patients after treatment for Cushing's disease, acromegaly, and

NFMA did not differ from each other with respect to coping strategies, besides the fact that patients with Cushing's disease sought more social support than patients treated for NFMA. This is an interesting difference that might be due to more severe long-term effects of Cushing's disease compared with NFMA. Patients after long-term remission of Cushing's disease suffer from subtle cognitive impairments, increased prevalence of psychopathology and an increased incidence of maladaptive personality traits (7, 17). These impairments could be invalidating in everyday life, which in turn could lead to a higher need for social support.

This is the first study that explored coping strategies in patients treated for Cushing's disease, acromegaly, or NFMA. There are, however, two previous studies by one research group that reported coping strategies in small groups of patients (Cushing's disease n=18, acromegaly n=17) during or less than 1yr after treatment in a developing country (15;16). However, it is not clear whether patients report different coping strategies compared with controls and whether the coping strategies reported by the patients are negative or positive.

The present study explored coping strategies in patients treated for Cushing's disease, acromegaly, or NFMA. We believe this is valuable information, since these are chronic diseases with multiple invalidations after cure (1-3;7;17-21), which are often misunderstood and difficult to treat. Following successful treatment of hypercortisolism in Cushing's disease, signs and symptoms of the disease disappear. However, a large number of studies in humans and animal models have documented that prolonged, increased endogenous or exogenous exposure to glucocorticoids may have long-lasting adverse effects on behavior and cognition, due to functional and structural alterations in specific brain target areas (7;17;22;23). Furthermore, in acromegaly, many of the systemic changes induced by previous excess of GH and/or IGF-I are not completely reversed upon successful biochemical treatment of active acromegaly (20), which may also be true for the effects of GH and/or IGF-1 on the central nervous system (24). Patients after treatment for Cushing's disease, acromegaly, or NFMA suffer from persistently impaired QoL (1-3). Knowledge on coping strategies used by these patients is of importance, since this information can be used in designing an intervention based on, for example cognitive behavioural therapy, self-management training, and information on the negative effects of the disease. We speculate that, with a targeted intervention, patients could be taught self-management skills and be better informed about the consequences of their disease. We believe that this might lead to an improved QoL. Such self-management and educational interventions are already offered to, for example, patients with inflammatory bowel disease (24) and patients after stroke (25).

A possible limitation of this study might be the fact that the most distressed sub-

jects may be more likely participate, which is known as the concept of symptomatic volunteers. This should be kept in mind when interpreting the conclusions of this study. However, conversely, it might also be possible that patients who feel worse are less likely to participate. It is difficult to assess this issue in detail. Nonetheless, there we no differences in clinical characteristics between patients who participated and those who decided not to participate in the current study. In addition, the differences found between pituitary patients and the reference groups were very large and there is, at least in this cohort of patients, an obvious need for a self-management intervention.

In summary, patients treated for Cushing's disease, acromegaly, or NFMA display different and less effective coping strategies compared with healthy controls. Compared with patients with chronic pain and patients receiving primary care psychology services, patients treated for pituitary adenomas report somewhat better coping strategies. These results strongly point towards the need to develop, to apply and to evaluate coping skills training and self-management in patients with this condition.

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