CLINICAL STUDY

Personality in patients with pituitary adenomas is characterized by increased anxiety-related traits: comparison of 70 acromegalic patients with patients with non-functioning pituitary adenomas and age- and gender-matched controls

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Abstract

Objective: Although neuropsychiatric and morphological brain alterations in acromegalic patients have been described and a distinct disease personality is clinically suspected, this has never been systematically investigated. We examined whether patients with acromegaly showed an altered personality profile compared with patients with non-functioning pituitary adenomas and healthy controls.

Design and methods: In this cross-sectional study, 70 acromegalic patients and 58 patients with non-functioning pituitary adenomas were compared with 140 mentally healthy population controls, matched for age and gender. Personality traits were measured by standardized personality questionnaires (Eysenck personality questionnaire-RK and tridimensional personality questionnaire).

Results: Compared with healthy controls, acromegalic patients described themselves as distinctly more harm avoidant and neurotic and presented themselves with high social conformity. On harm avoidant subscales, they reported more anticipatory worries and pessimism, higher fear of uncertainty, higher fatigability and asthenia. This personality pattern was not specific for acromegaly, but could similarly be observed in patients with non-functioning pituitary adenomas. However, specific for patients with GH-producing adenomas was an even more reduced novelty-seeking behaviour, especially in terms of lower impulsiveness, compared with patients with non-functioning pituitary adenomas.

Conclusion: Patients with pituitary adenomas show a distinct pattern of increased anxiety-related personality traits compared with the general population, potentially as a result of the pituitary lesion and/or associated hormonal dysregulations and comorbidities. Acromegaly is additionally associated with reduced impulsivity and novelty-seeking behaviour, which might affect patients' management and their quality of life.

European Journal of Endocrinology 160 367–373

Introduction

Pituitary lesions are suspected to alter mood and personality through direct and indirect interrelations with the prefrontal cortex and limbic structures (1). However, clinical studies on this topic are lacking. Since the middle of the last century, the associations of hormonal excess and deficiency syndromes with altered behaviour, psychopathology and personality have been investigated (2, 3), and from small-scale descriptive reports in the 50s, symptoms such as apathy, deceleration, fatigue and indifference have been specifically ascribed to acromegalic patients (4).

Recently, we reported a higher prevalence of affective disorders in acromegalic patients compared with patients with chronic somatic disorders and healthy controls (Sievers *et al.* unpublished observations). This

finding was associated with disturbances in the macroscopic brain tissue architecture with an increase in the grey and white matter volume at the expense of the cerebrospinal fluid (CSF) spaces (5). These clinical data supported *in vitro* and animal experiments identifying GH and insulin-like growth factor 1 (IGF1) as important hormones for brain function and development. In rodents, for instance, GH and IGF1 elicit active coping behaviour in the forced swim test (6). Through these central effects, it is conceivable that both the lack and excess of GH/IGF1 might alter personality.

Hence, we hypothesized that an altered personality profile of patients not only with pituitary adenomas but also with GH-producing adenomas (acromegalic patients) exists.

To test this hypothesis, we employed two established personality inventories: the Eysenck and the Cloninger

personality questionnaires (EPQ). According to Eysenck's personality theory, an individual can be described by three hierarchically organized 'super-factors' of personality: extraversion (antipole introversion), psychoticism (antipole impulse control) and neuroticism (antipole emotional stability) (7). An additional scale measures social conformity ('lie scale'). To capture these dimensions, the EPQ or its German short version EPQ-RK is commonly used (8, 9).

Cloninger postulated an alternative 'bisocial theory of personality' with three independent and genetically determined factors that are interpreted as stimulus-response systems related to certain neuroanatomical structures. The tridimensional personality questionnaire (TPQ) is the respective instrument, commonly used in clinical personality research (10, 11).

Subjects and methods

Participants

Patients with previously diagnosed acromegaly ($n = 70$) and with non-functioning pituitary adenomas ($n = 58$) as clinical control group were recruited at the Endocrine Outpatient Unit of the Max Planck Institute of Psychiatry and the Department of Internal Medicine, Ludwig-Maximilians-Universität in Munich in equal parts. As a normal population control group, we sampled 140 age- and gender-matched control subjects (ratio 1:2) from the Munich Antidepressants Response Signature project. All subjects gave their written informed consent. The study was approved by the local ethical committee.

Assessment of personality

Personality traits in the three study groups were assessed using two general questionnaires, the German versions of the EPQ-RK and the TPQ.

The EPQ-RK comprises of 50 items to be answered in a binary mode 'yes'/'no' (9). The responses define the three personality dimensions of psychoticism, extraversion and neuroticism, complemented by a social desirability scale.

The TPQ encompasses 100 items describing statements about habitual behaviour, which can be answered in a binary mode as 'I do agree'/'I do not agree' (11). The responses are summarized with respect to the three dimensions of personality (novelty seeking, harm avoidance and reward dependence), each of them encompassing four subscales: i) novelty seeking (TPQ-NS) with exploratory excitability (TPQ-NS1), impulsiveness (TPQ-NS2), extravagance (TPQ-NS3) and disorderliness (TPQ-NS4); ii) harm avoidance (TPQ-HA) with anticipatory worries and pessimism (TPQ-HA1), fear of uncertainty (TPQ-HA2), shyness with strangers (TPQ-HA3) and fatigability and

asthenia (TPQ-HA4); and iii) reward dependence (TPQ-RD) with sentimentality (TPQ-RD1), persistence (TPQ-RD2), attachment (TPQ-RD3) and dependence (TPQ-RD4).

The correlation between the EPQ-RK and the TPQ shows substantial correlations between some subscales such as novelty seeking and extraversion ($r = 0.53$) and novelty seeking and psychoticism ($r = 0.49$). Harm avoidance correlates positively with neuroticism ($r = 0.6$) and negatively with extraversion ($r = -0.42$), and reward dependence correlates positively with extraversion ($r = 0.45$) (12).

Assessment of comorbidities, biochemical variables and covariates

Clinical characteristics of the subjects were collected with regard to disease history, tumour characteristics, previous and present therapy and comorbidities as well as present complaints. Comorbidities were diagnosed according to the respective guidelines. In the case of missing data or uncertainty, additional information was obtained by file review.

Therapies used to treat acromegaly followed the consensus treatment algorithm proposed by Giustina and colleagues (13, 14). Drugs used in the case of recurrence or unsuccessful surgery included somatostatin analogues octreotide and lanreotide as first-line medical intervention (received by 35% of acromegalic patients at the study time point). In selected cases (i.e. only modest GH/IGF1 elevation or additional hyperprolactinemia), dopaminagonists, including cabergoline and bromocriptine, were used alone or in combination with somatostatin analogues (received by 12% of acromegalic patients at the study time point). In the cases of somatostatin analogue resistance or intolerance, the GH receptor antagonist pegvisomant was administered (received by 11% of acromegalic patients at the study time point).

Biochemical control in acromegalic patients was defined as (a) GH below $1 \mu\text{g/l}$ during a glucose tolerance test over 2 h, and (b) IGF1 level within two standard deviations of an age- and gender-adjusted normative sample. Twenty-four acromegalic patients (34.3%) did not fulfil the criteria of biochemical control in one of the parameters at the study time point (regarded as 'active acromegaly').

In all patients, basal fasting measurements of IGF1, TSH, free thyroxine (FT_4), total triiodothyronine (T_3), LH, FSH, prolactin and testosterone (in men) or oestradiol (in women) were performed, as well as stimulation tests such as a short ACTH test or the GHRH/arginine test in the case of suspected pituitary deficiencies in the corticotroph or somatotroph axis. All hormonal assessments were done between 0800 and 1000 h. The diagnosis of hypopituitarism was based on the criteria as reported earlier (15). All acromegalic patients with secondary hypoadrenalism,

hypothyroidism, hypoadrenalism and hypogonadism (47.5, 31.2, 45 and 2.6% respectively) and all patients with non-functioning pituitary adenomas and secondary hypoadrenalism, hypothyroidism, hypoadrenalism and hypogonadism (71.4, 66.7, 57.7 and 65.4% respectively) were studied while on optimized replacement therapy (including hydrocortisone, thyroid hormone, transdermal gonadal steroids or i.m. testosterone where appropriate).

Statistical analysis

Statistical analysis was performed using SPSS Version 16 for Windows. Sample characteristics were compared using χ^2 tests and analysis of variance. Differences in personality between the acromegalic patients, healthy controls and the clinical control group of patients with non-functioning pituitary adenomas were evaluated with an analysis of covariance (ANCOVA) controlling for age and gender. In the case of group differences, *post hoc* tests corrected for multiple comparisons following the Bonferroni–Holm procedure were applied (16). Differences between the clinical comparison groups were also analysed using ANCOVA, additionally controlling for i) adenoma type, pituitary deficiency and treatment history of surgery and radiation, as well as ii) adenoma type and comorbid disorders that differed between the patient groups (pituitary deficiency, cardiomyopathy, hypertension, arthralgia, arthropathy, carpal tunnel syndrome, diabetes mellitus, sleep apnoea; Table 1). In addition, we applied the Mann–Whitney U test to evaluate personality differences between biochemically controlled and uncontrolled acromegalic patients.

Results

Demographic and clinical characteristics of the study groups are presented in Table 1.

Subjects constituting the normal control group (population based) were matched for age and gender (1:2) with the acromegalic group. Acromegalic patients differed in some variables from the clinical control group consisting of patients with non-functioning pituitary adenomas: the acromegaly group included more females (55.7 vs 34.5%, $P=0.02$) and they were significantly younger (55.0 ± 11 vs 60.3 ± 10.6 years, $P=0.006$). There was no significant difference in respect to percentage of patients who had been operated or irradiated, but patients with acromegaly adenomas had lower prevalences of macroadenomas (68.6 vs 86.3%) and pituitary deficiencies of any axis (63.8 vs 88.2%). Regarding comorbidities, acromegalic patients suffered more often from cardiomyopathy, arthralgia, carpal tunnel syndrome, diabetes mellitus, pituitary deficiencies and sleep apnoea compared with patients

with non-functioning pituitary adenomas. However, the prevalence of other comorbidities such as hypertension, hyperprolactinemia, lung diseases or cancer did not differ between both groups.

For the control group, clinical characteristics such as adenoma type, treatment and biochemical control did not apply. However, prevalence rates of diabetes, hypertension and cancer were recorded also in normal controls, which, besides malignancies, occurred at lower rates than in patients.

Profile of personality traits in acromegaly compared with normal and clinical controls

Compared with normal controls, acromegalic patients described themselves as distinctly more neurotic (EPQ-N; $P<0.001$) and harm avoidant (TPQ-HA; $P<0.001$) in combination with a reduced novelty-seeking behaviour ($P=0.01$), but also presented themselves with high social conformity (EPQ-SD; $P<0.001$). Harm avoidance subscales suggest that the neurotic harm avoidant personality type is especially characterized by anticipatory worries and pessimism (TPQ-HA1), fear of uncertainty (TPQ-HA2), as well as fatigability and asthenia (TPQ-HA4) (all $P<0.001$). The results are summarized in Table 2. The neurotic and harm avoidant personality pattern, however, was not specific for acromegaly, but could be similarly observed in patients with non-functioning pituitary adenomas compared with controls.

Acromegalic patients differed from patients with non-functioning pituitary adenomas in a particular domain: they showed a more pronounced reduction in novelty-seeking behaviour ($P=0.04$), especially in terms of a lower impulsiveness ($P=0.01$). This difference remained significant when adjusted for age, gender, adenoma type (macro/microadenomas), history of surgery, history of radiation and pituitary deficiency ($P=0.028$), suggesting a specific involvement of acromegalic features (GH/IGF1 excess or associated morbidities) for this effect. This effect was also replicated after all clinical variables that showed a significant difference between these two groups (adenoma type, presence of pituitary deficiency, cardiomyopathy, hypertension, arthralgia, arthropathy, carpal tunnel syndrome, diabetes mellitus or sleep apnoea; Table 1) were additionally included as covariates ($P=0.032$).

However, acromegalic patients who were treated and biochemically controlled (defined as having GH and IGF1 levels within the normal range) displayed lower impulsivity scores (2.37 ± 1.76) than those with persistent GH/IGF1 excess (3.30 ± 1.46 , $P=0.016$), which contradicts the hypothesis of a direct connection between the neuroendocrine activity of the pituitary adenomas and this particular personality trait.

Additionally, comparing the scores of the deviant personality scales between all patients with micro- and

Table 1 Clinical characteristics of study population including 70 acromegalic patients, 140 age- and gender-matched controls and 58 patients with non-functioning pituitary adenomas.

	Acromegalic patients		Controls normal population		Non-functioning pituitary adenoma patients		Statistical tests		Bonferroni–Holm-corrected <i>post hoc</i> tests		
	(1)		(2)		(3)				(1) vs (2)	(1) vs (3)	(2) vs (3)
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	χ^2	<i>P</i> value	<i>P</i> value	<i>P</i> value	<i>P</i> value
Male	31	44.3	62	44.9	38	65.5	8.20	0.017	ns	0.02	0.007
Female	39	55.7	76	55.1	20	34.5					
	Mean	s.d.	Mean	s.d.	Mean	s.d.	ANOVA	<i>P</i> value	<i>P</i> value	<i>P</i> value	<i>P</i> value
Age	55.0	11.0	55.0	11.0	60.3	10.6	5.35	0.017	ns	0.006	0.009
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	χ^2	<i>P</i> value	<i>P</i> value	<i>P</i> value	<i>P</i> value
Adenoma type											
Macroadenoma	48	68.6	NA	NA	50	86.3	5.50	0.019			
Microadenoma	7	10.0	NA	NA	4	6.9	0.39	ns			
Unknown	15	21.4	NA	NA	4	6.9	5.30	0.021			
Treatment											
Surgery	65	92.9	NA	NA	52	96.3	0.71	ns			
Radiotherapy	19	27.1	NA	NA	15	28.3	0.01	ns			
Comorbidities											
Pituitary deficiency of any axis	44	63.8	NA	NA	45	88.2	9.16	0.002			
Hyperprolactinemia	7	10.6	NA	NA	2	4.5	1.29	ns			
Cardiomyopathy	9	12.9	NA	NA	0	0	8.00	0.005			
Cerebrovascular diseases	4	5.7	NA	NA	3	5.5	0.01	ns			
Hypertension	38	54.3	39	28.3	27	46.6	16.59	<0.001	<0.001	ns	0.016
Coronary artery disease	6	8.6	NA	NA	2	3.6	1.36	ns			
Myocardial infarction	1	1.4	NA	NA	1	1.8	0.02	ns			
Arthralgia	46	66.7	NA	NA	25	44.6	6.11	0.013			
Arthropathia	24	34.8	NA	NA	9	17.3	4.57	0.033			
Carpal tunnel syndrome	34	49.3	NA	NA	11	20	11.35	0.001			
Diabetes mellitus	19	27.9	6	4.3	6	10.5	22.34	<0.001	<0.001	0.034	ns
Sleep apnoea	23	33.3	NA	NA	6	10.7	8.77	0.003			
Other lung diseases	5	7.2	NA	NA	1	1.8	2.08	ns			
Malignancies	8	11.8	8	5.8	6	10.5	3.46	ns			

Significant effects are shown in bold.

Table 2 Personality traits in the study population.

	Acromegalic patients		Controls normal population		Non-functioning pituitary adenoma patients		ANCOVA		Bonferroni–Holm-corrected <i>post hoc</i> tests		
	(1)		(2)		(3)				(1) vs (2)	(1) vs (3)	(2) vs (3)
	Mean	S.D.	Mean	S.D.	Mean	S.D.	<i>F</i> (2;140)	<i>P</i> value	<i>P</i> value	<i>P</i> value	<i>P</i> value
Eysenck personality questionnaire (EPQ-RK)											
Psychoticism (EPQ-P)	1.89	2.00	1.82	1.49	1.34	1.46	1.03	ns			
Extraversion (EPQ-E)	5.51	3.06	6.0	3.43	5.91	3.84	0.81	ns			
Neuroticism (EPQ-N)	4.45	3.19	2.71	1.91	4.02	2.80	12.95	<0.001	<0.001	ns	<0.001
Social desirability (EPQ-SD)	5.23	3.08	3.59	2.20	5.76	2.75	15.25	<0.001	<0.001	ns	<0.001
Cloninger temperament and personality questionnaire (TPQ)											
TPQ novelty-seeking total (TPQ-NS)	12.49	4.96	14.75	4.93	13.49	4.83	5.24	0.01	<0.001	0.04	ns
Exploratory excitability (TPQ-NS1)	3.39	2.06	4.23	1.88	3.65	1.83	4.5	0.01	<0.001	ns	ns
Impulsiveness (TPQ-NS2)	2.64	1.73	3.49	2.0	3.44	2.12	5.30	0.01	<0.001	0.01	ns
Extravagance (TPQ-NS3)	3.18	1.58	3.8	1.67	3.37	1.50	3.91	0.02	0.01	ns	ns
Disorderliness (TPQ-NS4)	3.29	1.80	3.21	1.76	3.00	1.57	0.09	ns			
TPQ harm avoidance total (TPQ-HA)	15.61	7.06	11.19	5.60	15.63	6.81	17.3	<0.001	<0.001	ns	<0.001
Anticipatory worries and pessimism (TPQ-HA1)	4.39	2.51	3.4	2.20	4.25	2.49	6.03	<0.001	<0.001	ns	0.01
Fear of uncertainty (TPQ-HA2)	4.57	1.90	3.57	1.98	4.40	1.82	8.32	<0.001	<0.001	ns	0.006
Shyness with strangers (TPQ-HA3)	2.67	1.90	2.26	1.75	2.82	1.86	2.08	ns			
Fatigability and asthenia (TPQ-HA4)	4.0	3.0	1.95	1.82	4.14	2.66	26.67	<0.001	<0.001	ns	<0.001
TPQ reward dependence total (TPQ-RD)	16.5	3.61	15.72	4.47	15.56	3.69	0.88	ns			
Sentimentality (TPQ-RD1)	4.04	1.01	3.85	1.25	3.95	1.17	0.75	ns			
Persistence (TPQ-RD2)	3.73	2.13	3.62	2.10	3.54	1.86	0.07	ns			
Attachment (TPQ-RD3)	6.17	2.29	5.81	2.6	5.70	2.28	0.57	ns			
Dependence (TPQ-RD4)	2.54	1.50	2.45	1.45	2.37	1.41	0.33	ns			

Results of the Eysenck personality questionnaire (EPQ-RK) and the Cloninger temperament and personality questionnaire (TPQ) are compared between groups using ANCOVA adjusted for age and gender. Bonferroni–Holm-corrected *post hoc* tests for two-group comparisons are performed in the case of significant differences in the global ANCOVA. Significant effects are given in boldface. ANCOVA adjusted for age and gender.

macroadenomas or with and without pituitary deficiency, we did not find significant differences ($P > 0.05$).

Discussion

In this study, we aimed to investigate whether acromegalic patients show a distinct personality profile measured by the EPQ-RK and TPQ questionnaires compared with a normal population. To differentiate the specific effects of acromegaly characterized by a chronic GH/IGF1 excess, we additionally contrasted against a 'clinical' control group consisting of patients with non-functioning pituitary adenomas.

We found that i) the personality of patients with pituitary adenomas show a distinct pattern of increased anxiety-related, 'neurotic' personality traits compared with the general population, and ii) patients with GH-producing adenomas (acromegalic patients) showed reduced novelty seeking, especially in terms of less impulsive behaviour compared with patients with non-functioning pituitary adenomas. This finding could be replicated with comparable effect size (Cohen's $f = 0.25$, original analysis: $f = 0.27$) after controlling for the effects of the adenoma type and of comorbid disorders (17).

The reason for the observed change could lay in direct or indirect effects of the pituitary lesion or hormonal disturbances on neural circuits or neurotransmission (1). Weitzner *et al.* proposed that the hypothalamic-pituitary axis may affect behavioural control exerted by the prefrontal cortex through its rich connections with limbic structures. Also cortical-striatal-thalamic-cortical circuits associated with apathy and receiving afferent input from the hypothalamic-pituitary tract may be involved (18).

We do not know why acromegalic patients show reduced novelty-seeking behaviour and less impulsiveness than patients with non-functioning pituitary adenomas. Matsuo and colleagues reported that the grey matter volume of the ventromedial prefrontal region (VMPFC), particularly the orbitofrontal region, is inversely correlated with impulsivity scores (19). It could be hypothesized that the global enlargement of the grey matter in acromegalic patients (5) encompasses the VMPFC and subsequently translates into a decrease in impulsiveness. In concordance with the results of this study, the grey and white matter alterations in acromegalic patients were not directly correlated with actual GH/IGF1 level (biochemical control).

However, since this is a cross-sectional design, we are not able to draw conclusions between the causal relationship of acromegaly and associated changes and the development of personality alterations. This has to be further elucidated in the studies with prospective designs.

Nevertheless, we can conclude that the altered personality profile observed in patients with pituitary

adenomas, and specifically acromegaly, might potentially influence important areas such as the patients' quality of life, treatment adherence and patient-doctor contact.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

Funding

This work was supported by an independent research grant from Pfizer Pharma GmbH, Karlsruhe, Germany (to G K Stalla and C Sievers). G K Stalla received lecture fees from Pfizer Pharma GmbH, Karlsruhe, Germany; Novo Nordisk Pharma GmbH, Germany; Ipsen International GmbH, Germany; and Novartis Pharma GmbH, Germany. C Sievers received lecture fees from Pfizer Pharma GmbH, Karlsruhe, Germany, and Novartis Pharma GmbH, Germany.

Acknowledgements

We thank Iris Miedl, Doris Goy-Alsing and Sylvia Lang for their valuable contributions in helping to process the patient data.

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Received 19 November 2008

Accepted 2 December 2008