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ORIGINAL ARTICLE

Prevalence of mental disorders in acromegaly: a cross-sectional study in 81 acromegalic patients

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Summary

Objective Emotional and behavioural alterations have been described in acromegalic patients. However, the nature and psychopathological value of these changes remained unclear.

We examined whether acromegalic patients have an increased prevalence of comorbid DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Version) mental disorders in comparison to subjects with or without chronic somatic disorders.

Design/patients A cross-sectional study was conducted at the Max-Planck Institute of Psychiatry and the Ludwig-Maximilians-University Munich. Eighty-one acromegalic patients were enrolled. Control subjects with (n = 3281) and without chronic somatic (n = 430) disorders were drawn from a representative sample of the German adult general population as part of the Mental Health Supplement of the German Health Interview and Examination Survey. Lifetime and 12-month prevalences of DSM-IV mental disorders were assessed with face-to-face interviews using the standardized German computer-assisted version of the Composite International Diagnostic Interview.

Results Acromegalic patients had increased lifetime rates of affective disorders of 34·6% compared to 21·4% in the group with chronic somatic disorders (OR = 2·0, 95% CI 1·2–3·2) and to 11·1% in the group without chronic somatic disorders (OR = 4·4, 95% CI 2·3–8·7). Affective disorders that occurred significantly more often than in the control groups began during the putative period of already present GH excess. Higher rates of DSM-IV mental disorders were reported in those patients with additional treatment after surgery.

Conclusion Acromegaly is associated with an increased prevalence and a specific pattern of affective disorders. Greater emphasis on diagnosing and treatment of mental disorders in acromegalic patients might improve the disease management.

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Introduction

In acromegalic patients, the long-lasting excess of GH and insulin-like growth factor (IGF-1) leads to a considerable range of morbid conditions, such as organomegaly, facial disfigurement, arthropathy, respiratory diseases, diabetes mellitus, hypertension, pituitary deficiency and a variety of neurological complications, such as nerve compression syndromes.[1] Among these morbid complications, it remains unclear as to what degree acromegalic patients also suffer from an increased rate of mental disorders, as defined by modern diagnostic criteria like Diagnostic and Statistical Manual of Mental Disorders, 4th Version (DSM-IV).

The first attempts to characterize neuropsychiatric disturbances in acromegalic patients date back to the 19th century when the disease was described by Pierre Marie.[2] The Swiss psychiatrists Bleuler and Blickenstorfer tried to describe a distinct pattern of 'personality' of patients with pituitary diseases such as Cushing's disease and acromegaly.[3–7] They established the term 'endocrine psychosyndrome' in the middle of the 20th century. In the following decades, a limited number of clinical studies have been carried out to further investigate the personality and psychopathology of patients with pituitary adenomas and hormonal excess.[8–14]

These studies were tainted with methodological problems such as the use of the poorly defined term of 'personality', as well as partly idiosyncratic terms for psychopathology, mixed study populations (patients with different pituitary adenomas), lack of control groups, standardized tools or sufficient patient numbers. However, all authors suggested at least some evidence for increased rates of psychopathological disturbances and certain personality characteristics in acromegalic patients. One of the most comprehensive studies on neuropsychiatric aspects in acromegalic patients was

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performed by Richert *et al.* on 31 acromegalic patients. The authors reported a high number of tidy, arduous and assiduous persons in the group of acromegalic patients.[8] Psychopathological symptoms in most of these patients comprised loss of drive, concentration and libido.

However, the quantity and quality of these features remain unclear until today. This is mostly due to the lack of studies using modern psychopathological syndrome scales, and the lack of diagnostic interviews providing a reliable description of psychopathological features and mental disorders according to the criteria of the International Classification of Diseases, 10th Revision or DSM-IV. Thus, it remains unclear whether acromegalic patients are at an increased risk of mental disorders, or whether they are simply distressed below the threshold of clinically significant psychopathological syndromes because of their illness, the complications or the treatment.

Increased attention to specific neuropsychiatric comorbidity in acromegaly might be particularly relevant given that preclinical research has provided new insights into the role of GH and IGF-1 in brain function. Both factors possess multiple functions in the neuronal system and play key roles in the development of the brain including cell differentiation and survival, inhibition of apoptosis, mediation of cell cycle progression and modulation of the immune response.[15–19] Such neurotrophic functions may also underlie the protective effects observed in animal models of brain ischaemia or depression.[20]

However, whether long-term GH and IGF-1 excess alters the psychopathological risk profile in acromegalic patients, possibly by influencing brain morphology or function, is not known.

Against this background, the present study examines the rate of mental disorders according to the criteria of DSM-IV in patients with biochemically confirmed acromegaly. We compared these patients to two control groups, sampled from community surveys.

Further, the study explored possible specific patterns of psychopathology in subgroups of acromegalic patients characterized by treatment modalities or comorbidities.

Subjects and methods

Study design

The study was performed as a cross-sectional diagnostic study comparing 81 acromegalic patients, 3281 control subjects with and 430 control subjects without chronic somatic disorders. Participants were consecutively scheduled and interviewed using the Composite International Diagnostic Interview for DSM-IV (DIA-X/M-CIDI) after the clinical evaluation.

Acromegalic patients

For the purpose of this study, 145 patients, over 18 years of age, with previously diagnosed acromegaly that had been treated during the past 6 years at either the Endocrine Outpatient Unit of the Max-Planck Institute of Psychiatry or the Department of Internal Medicine, Ludwig-Maximilians-University Munich, were identified by the electronic data processing system of the respective hospitals in March 2006. These patients were contacted by a letter describing the aim and design of the presented study. Nonresponders were further encouraged to participate by phone. A total of 81 patients participated (response rate 56%). Reasons for nonparticipation were relocation and distance to study centre, unwillingness to spend time and effort on examinations, and other reasons. Exclusion criteria were the inability or unwillingness to perform the psychopathological assessments (i.e. insufficient language skills, diagnosed dementia). After complete description of the study to the subjects, written informed consent was obtained. The patients were consecutively scheduled and included into the study at the outpatient clinics of both institutes from April 2006 through July 2007.

The project was approved by the local ethics committees.

Controls

The control subjects were drawn from a representative sample of the German adult general population who participated in the German National Health Interview and Examination Survey–Mental Health Supplement (GHS–MHS), a community survey of the German general population.[21,22] This study was conducted under the responsibility of one of the authors (HUW) using identical assessment forms and instruments (CIDI) and applying the same diagnostic criteria and algorithms. Control subjects reporting one or more chronic somatic disorders such as diabetes, cardiovascular disease or cancer were defined as 'chronically ill control group' ($n = 3281$), while subjects without somatic morbidities were defined as somatically healthy controls.

Clinical characterization and laboratory measurements

The clinical characteristics of the participants at the time of study participation are described in Table 1. As part of a standardized clinical assessment, including a physical examination and laboratory analyses, all acromegalic patients were systematically evaluated for tumour characteristics determined by magnetic resonance imaging including a specific sellar protocol including contrast medium. Visual field defects at the time of diagnosis were reported. Additionally, history of treatment (surgery, radiotherapy and medication), history of comorbidities including cardiovascular features, metabolic features, respiratory features, bone and joint features, malignancies and endocrine consequences such as thyroid goitre and pituitary deficiencies, past medical history and actual symptoms were reported. Additional information was obtained from the patients' files in the case of missing data or if data sources were unclear. We measured basal hormonal levels, as well as metabolic parameters, in all patients (between 8:00 and 10:00 am) in a fasting state on the day of study participation.

The current biochemical disease control was evaluated based on the consensus criteria with (a) GH below 1 μg/l during a glucose tolerance test over 2 h (if available), and (b) IGF-1 within two standard deviations of an age- and gender-adjusted normative range.[23] Serum concentrations of GH were measured using the automated Advantage chemiluminescent assay system

Table 1. Demographic and clinical characteristics of acromegalic patients and controls

	Acromegalic patients Group 1 (N = 81)	Percent	Controls with chronic somatic disorders Group 2 (N = 3281)	Percent	Controls without chronic somatic disorders Group 3 (N = 430)	Percent	Group 1 *vs.* 2	Group 1 *vs.* 3
Age								
Mean age ± SE	54·7 ± 1·4		45·1 ± 0·2		37·9 ± 0·5		<0·01	<0·01
Gender								
Male	38	46·9	1368	46·6	302	74·2	NS	NS
Female	43	53·1	1913	53·4	128	25·8	NS	NS
Educational status								
<10 years	41	50·6	1315	44·4	144	37·3		
10–11 years	20	24·7	1208	34·3	163	34·7		
12 + years	20	24·7	697	21·3	114	28·0	NS	NS
Legal status								
Single	17	21	443	14·7	118	31·7		
Married	47	58	2420	75·1	267	61·9		
Divorced	10	12·4	245	6·8	31	5·5		
Widowed	7	8·6	114	3·4	4	0·9	<0·01	<0·01
Primary adenoma type								
Macro	53	65						
Micro	6	7						
Unknown size of primary GH-secreting adenoma	22	28						
Treatment								
Surgery	73	90·1						
Mean time after surgery in years ± SE	10·15	0·88						
Radiotherapy	20	24·7						
Mean time after radiotherapy in years ± SE	9·1	1·61						
History of medical treatment	44	54·3						
Currently under DA	10	12·3						
Currently under SRLs	28	34·6						
Currently under pegvisomant	9	11·1						
Surgery, radiotherapy and medical therapy	18	22·2						
Biochemical control study time point								
Controlled	47	58						
Uncontrolled	34	42						
Mean GH μg/l ± SE*	2·8	0·59						
Mean IGF-1 μg/l ± SE	214·2	18·0						
Comorbidities (lifetime)								
Arrhythmias	16	19·8						
Cardiomyopathy	9	11·1						
Cerebrovascular diseases	4	4·9						
Hypertension	43	53·1						
Coronary artery disease	7	8·6						
Myocardial infarction	1	1·2						
Arthralgia	53	65·4						
Arthropathia	26	32·1						
Carpal tunnel syndrome	37	45·7						
Diabetes mellitus	22	27·2						
Pituitary deficiency	48	59·3						
Hyperprolactinaemia	7	8·6						
Sleep apnoea	28	34·6						
Other lung diseases	5	6·2						
Malignancies	9	11·2						
Psychopathological information								
Utilization of health care system for mental health	26	32·1						
Antidepressant drug intake (lifetime)	6	7·4						
Symptoms at study time point								
Acromegalic growth	12	14·8						

Table 1. (*Continued*)

	Acromegalic patients Group 1 ($N = 81$)	Percent	Controls with chronic somatic disorders Group 2 ($N = 3281$)	Percent	Controls without chronic somatic disorders Group 3 ($N = 430$)	Percent	Group 1 *vs.* 2	Group 1 *vs.* 3
Arthralgia	49	60·5						
Tiredness	41	50·6						
Headache	25	30·9						
Sleep apnoea	28	34·6						
Paraesthesia	39	48·1						
Sweating	29	35·8						
Visual disturbances	19	23·5						

DA, dopamine agonist therapy; SRLs, somatostatin receptor ligand therapy; NS, not significant.
*Patients receiving pegvisomant are excluded from this analysis.

(Nichols Diagnostics Institute, Bad Vilbel, Germany) and IGF-1 was measured by automated chemiluminescent assays (IMMULITE® 2000, Siemens Healthcare Diagnostics, Germany). Somatic comorbidities of acromegaly were diagnosed according to standard diagnostic procedures. Therapies used to treat acromegaly followed the consensus treatment algorithm proposed by Giustina and colleagues.[24,25] Aims of the therapy encompass (i) biochemical control defined as GH in an oral glucose tolerance test <1 μg/l and IGF-1 in the age- and gender-specific normal range, (ii) tumour mass reduction and (iii) the reduction of mortality, morbidity and symptoms.[24] Drugs that were used in case of recurrence or unsuccessful surgery included somatostatin analogues including octreotide and lanreotide as first-line medical intervention. In selected cases (i.e. only modest GH/IGF-1 elevation or additional hyperprolactinaemia), dopamine agonists including cabergoline and bromocriptine were used alone or in combination with somatostatin analogues. In cases of somatostatin analogue resistance or intolerance, the GH-receptor antagonist pegvisomant was administered.

Psychopathological assessment with the DIA-X/M-CIDI

Psychopathological assessments in all patients and the controls were based on face-to-face standardized diagnostic interviews (mean duration 90 min) by a clinically trained interviewer using the Composite International Diagnostic Interview for DSM-IV (DIA-X/M-CIDI), a modified version of the World Health Organization CIDI, version 1·2. Diagnostic assessment was based on the criteria of DSM-IV and further specific questions to cover characteristic acromegaly symptoms were added in a separate module.[26]

The interview included different sections encompassing questions about anxiety, depression, mania, eating disorders, substance abuse and obsessive-compulsive disorders. Each section started with some stem questions to screen for symptoms in the respective area followed by questions regarding onset, duration and severity of the symptoms. Example questions within the depression section are: 'Now I want to ask you about shorter periods of feeling depressed. In your lifetime, have you ever had two weeks or more when nearly every day you felt sad, blue, empty or depressed most of the day?' or 'Has there ever been 2 weeks or longer when you lost interest in most things like work and hobbies, or didn't you enjoy things you usually liked to do for fun?'.

With the responses to the DIA-X/M-CIDI, a classification of symptoms and diagnoses according to DSM-IV criteria of specific mental disorders (12-month and lifetime) along with information about onset, longitudinal course and severity can be made using an algorithm published earlier.[26]

For the purpose of this study, we evaluated the prevalence rates of any mental disorder. However, due to partially very low base rates, we focussed on affective and anxiety disorders. For the latter, we also used the so-called somatic exclusionary roles of the CIDI, assigning the diagnosis of anxiety, or affective disorder due to a general medical factor, in all cases where the clinician rated the occurrence of the mental disorder to be exclusively due to an established general medical factor. The interviewer was monitored throughout the entire study period and the finally obtained DIA-X/M-CIDI data went through an editing process. Acromegalic patients who were suspected to suffer from a clinical psychopathologic condition (as judged by the trained interviewer) were advised to consult a psychiatrist.

Statistical analyses

A priori power calculation suggested a sample size of 44 patients to detect prevalence differences of larger than 8% with a test power of larger than 80%, if a type I error of 0·05 is assumed. To perform further subgroup analyses in the group of acromegalic patients, we decided to increase the final sample size to >80 patients.

The data analysis was completed using Stata Statistical Software. Statistical weighting procedures were used to compensate for the oversampling of probands and to adjust the sample to match for age, sex and regional distribution of the national administrative statistics in Germany.[22,27] To carry out a correct weighing and stratification of the random samples, the STATA SVY (survey) commands were used. Based on the weighted 12-month and lifetime prevalence rates, the study groups were compared by logistic regression, controlling for age and gender. Regression coefficients

Table 2. Lifetime and 12 month prevalence of selected DSM-VI mental disorder diagnoses in acromegalic patients and control groups

	Acromegalic patients ($N = 81$)		Controls with chronic somatic disorders ($N = 3281$)		Controls without chronic somatic disorders ($N = 430$)		Acromegalic patients *vs.* controls with chronic somatic disorders			Acromegalic patients *vs.* controls without chronic somatic disorders		
	N	%	*N*	%w	*N*	%w	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Lifetime prevalence												
Any mental disorder	37	45·7	NA		NA		NA			NA		
Any affective	28	34·6	789	21·4	56	11·1	**2·0**	1·2–3·2	**0·006**	**4·4**	2·3–8·7	**0·000**
Any MDE (incl GMC)	23	28·4	699	19·0	50	9·7	**1·7**	1·1–2·8	**0·043**	**3·7**	1·9–7·6	**0·000**
MDE	15	18·5	618	16·7	47	9·2	1·1	0·6–2·1	0·659	2·2	1·0–4·7	0·053
MDE (GMC)	8	9·9	81	2·3	3	0·5	**4·1**	1·8–9·4	**0·001**	**26·4**	6·9–101·0	**0·000**
Dysthymia	13	16·1	205	5·2	7	1·5	**3·1**	1·7–6·0	**0·000**	**12·2**	3·7–40·3	**0·000**
Any panic disorder	0	0	180	4·5	8	1	**NA**[1]		**0·001***	NA[4]		0·273*
Panic disorder	0	0	173	4·4	8	1	**NA**[2]		**0·002***	NA[5]		0·273*
Panic Attack	0	0	355	9·1	18	2·9	**NA**[3]		**0·000***	NA[6]		0·078*
12 month prevalence												
Any mental disorder	24	29·6	822	21·7	56	10·7	1·6	0·98–2·6	0·061	**2·6**	1·3–5·3	**0·007**
Any affective	17	21·0	485	13·3	24	4·9	1·7	0·99–3·1	0·056	**4·8**	2·0–11·3	**0·000**
Any MDE (incl GMC)	12	14·8	390	10·7	19	3·7	1·5	0·8–2·8	0·260	**3·8**	1·5–9·7	**0·005**
MDE	6	7·4	344	9·5	18	3·6	0·8	0·3–1·8	0·563	1·7	0·6–5·4	0·345
MDE (GMC)	6	7·4	46	1·3	1	0·1	**5·7**	2·2–14·8	0·000	**71·1**	9·7–521·4	**0·000**
Dysthymia	13	16·1	205	5·3	6	1·3	**3·1**	1·7–6·0	0·000	**14·0**	4·0–49·5	**0·000**
Any anxiety	11	13·6	570	14·5	37	6·7	0·99	0·5–1·9	0·982	1·4	0·6–3·7	0·445
Any agoraphobia (incl GMC)	2	2·5	74	1·8	6	0·7	0·8	0·2–3·2	0·735	1·2	0·2–6·5	0·883
Any panic disorder	0	0	106	2·7	6	0·6	**NA**[7]		**0·033***	NA[12]		0·323*
Panic attack	0	0	202	5·2	11	1·4	**NA**[8]		**0·036***	NA[13]		0·323*
Any social phobia (incl GMC)	0	0	65	1·6	3	0·3	**NA**[9]		**0·000***	NA[14]		0·189*
Any GAD (incl GMC)	5	6·2	111	2·9	3	0·6	2·2	0·8–5·6	0·122	7·8	0·8–73·3	0·072
OCD	0	0	30	0·7	2	0·4	NA[10]		0·357*	NA[15]		0·602*
Any substance	2	2·5	418	12·5	61	13·7	0·2	0·1–1·1	0·059	**0·2**	0·1–0·9	**0·041**
Any eating disorder	0	0	9	0·3	2	0·4	NA[11]		0·631*	NA[16]		0·557*

In bold: significant results ($P < 0·05$); NA, not applicable due to empty cells or data not available.
*In the case of empty cells where a logistic regression could not be performed, a Pearson Chi-square Statistic with the Rao and Scott correction, design-based *F* and *P*-value is reported indicated by a '*' with further details reported below:
NA[1]: Design-based $F(1, 3359) = 10·73$; $P = 0·001$.
NA[2]: Design-based $F(1, 3359) = 10·09$; $P = 0·002$.
NA[3]: Design-based $F(1, 3359) = 34·78$; $P = 0·000$.
NA[4]: Design-based $F(1, 508) = 1·21$; $P = 0·273$.
NA[5]: Design-based $F(1, 508) = 1·21$; $P = 0·273$.
NA[6]: Design-based $F(1, 508) = 3·11$; $P = 0·078$.
NA[7]: Design-based $F(1, 3359) = 4·54$; $P = 0·033$.
NA[8]: Design-based $F(1, 3359) = 4·41$; $P = 0·036$.
NA[9]: Design-based $F(1, 3359) = 13·11$; $P = 0·000$.
NA[10]: Design-based $F(1, 3359) = 0·85$; $P = 0·357$.
NA[11]: Design-based $F(1, 3359) = 0·23$; $P = 0·631$.
NA[12]: Design-based $F(1, 508) = 0·98$; $P = 0·323$.
NA[13]: Design-based $F(1, 508) = 0·98$; $P = 0·323$.
NA[14]: Design-based $F(1, 508) = 1·73$; $P = 0·189$.
NA[15]: Design-based $F(1, 508) = 0·27$; $P = 0·602$.
NA[16]: Design-based $F(1, 508) = 0·35$; $P = 0·557$.

were transformed into odds ratios that are presented with their respective 95% CIs (Table 2). Additionally, we stratified by gender and calculated OR for each group with 95% CIs adjusted for age. Subgroup analyses within the acromegalic patient group were performed by logistic regression adjusted for age and gender.

Results

Demographic, clinical and social characteristics of the study participants and both control groups are presented in Table 1. Acromegalic patients differed in several sociodemographic variables from

either or both control groups: they were significantly older ($P < 0{\cdot}01$ for the comparisons with controls with and without chronic somatic disorders), more often widowed (acromegalic patients *vs.* controls with chronic somatic disorders $P < 0{\cdot}01$, and acromegalic patients *vs.* controls without chronic somatic disorders $P < 0{\cdot}01$). No significant differences were found with regard to the years of schooling.

Because of these sociodemographic differences, all subsequent analyses were controlled for age and gender.

Lifetime and 12-month prevalence of DSM-IV mental disorders in acromegaly compared to population controls with and without chronic somatic disorders

Table 2 reports on the prevalence rates of mental disorders of all groups, including any mental, affective and anxiety disorders, as well as the differential diagnostic breakdown for the latter. It should be noted that because of comorbidity, subjects could have had more than one disorder. To evaluate differences between groups, regression analyses controlling for age and gender were conducted.

Any mental disorder. The rate of lifetime DSM-IV mental disorder prevalence in the acromegalic group was as high as 45·7%. However, it has to be noted that the comparison of the lifetime prevalence of all mental disorders between control subjects and acromegalic patients could not be performed, because the Mental Health Supplement of the German Health Interview and Examination Survey (control group data) was not as comprehensive as for the acromegalic patient group. For any 12-month prevalence of DSM-IV diagnosis, acromegalic patients presented with a significantly higher rate of mental disorders compared to the control group without chronic somatic disorders (29·6% *vs.* 10·7%; OR = 2·6, 95% CI 1·3–5·3). Compared to the group with chronic somatic disorders, the difference did not reach significance (OR = 1·6, 95% CI 0·98–2·6).

Affective disorders. Acromegalic patients reported an increased rate of lifetime affective disorders compared to controls with chronic somatic disorders (34·6% *vs.* 21·4%; OR = 2·0, 95% CI 1·2–3·2) (Table 2). This was mainly attributable to major depression episodes (MDE) due to the general medical condition (GMC) and dysthymia (9·9% *vs.* 2·3%; OR = 4·1, 95% CI 1·8–9·4 and 16·1% *vs.* 5·2%; OR = 3·1, 95% CI 1·7–6·0, respectively). Compared to control subjects without chronic somatic disorders, the effects were more pronounced: the odds ratio was 4·4 for all affective disorders (95% CI 2·3–8·7), 26·4 for MDE GMC (95% CI 6·9–101·0) and 12·2 for dysthymia (95% CI 3·7–40·3), respectively.

For 12-month prevalences, acromegalic patients also reported higher rates for MDE GMC and dysthymia, compared to controls with chronic somatic diseases (7·4% *vs.* 1·3% with OR = 5·7, 95% CI 2·2–14·8; and 16·1% *vs.* 5·3% with OR = 3·1, 95% CI 1·7–6·0) that were even more emphasized compared to controls without chronic somatic diseases (7·4% *vs.* 0·1% with OR = 71·1 95% CI 9·7–521·4; and 16·1% *vs.* 1·3% with OR = 14·0, 95% CI 4·0–49·5) (Table 2).

Anxiety disorders. Compared to both control groups, anxiety disorders (including panic attacks and panic disorders for lifetime prevalence and any anxiety, general anxiety disorder for 12-month prevalence) did not occur more often in acromegalic patients. On the contrary, panic disorders and panic attacks were less frequent in acromegalic patients than in controls with chronic somatic disease. Due to the fact that no acromegalic patient in the study had ever suffered from a panic attack or panic disorder, logistic regression with OR could not be reported. Instead, a Pearson Chi-square Statistic with the Rao and Scott correction, design-based $F(1,3342) = 11{\cdot}3302$, $P = 0{\cdot}0008$ is reported. All differences between lifetime prevalence for any panic disorder and panic attack between acromegalic patients and control subjects with chronic somatic disorders were significant (Table 2). The same trend was seen for 12-month prevalences. There was no difference between controls without chronic somatic diseases and acromegalic patients.

Separate evaluation for male and female patients. Since affective disorders are gender-dependent with female patients being at higher risk of suffering from MDE and dysthymia during lifetime, we additionally stratified the analysis for females and males. Table 3 reports on the rate for those affective disorders that had shown significantly higher prevalence in the acromegalic group compared to the control groups (Table 2).

For female acromegalic patients, rates of lifetime affective disorders, MDE (GMC) and dysthymia as well as 12 months MDE (GMC) and dysthymia were in a similar range as for the whole group (Table 3). Male acromegalic patients showed similar rates of affective disorders compared to healthy controls, but the analyses revealed some different results compared to the controls with chronic somatic disorders: whereas lifetime dysthymia as well as MDE (GMC) and dysthymia were still significantly different between the groups, any affective and any MDE (incl GMC) were not different between these groups anymore (23·7% *vs.* 14·5% with OR = 1·8, 95% CI 0·9–4·1; and 18·4% *vs.* 12·2% with OR = 1·7, 95% CI 0·7–3·9). However, it should be noted that this could be due to the reduced sample size.

Temporal relationship between acromegaly onset and mental disorders

The analysis of age-of-onset characteristics of mental disorders revealed that, in most of the patients, the mental disorders (retrospectively determined age of onset) occurred before the acromegaly diagnosis (Fig. 1). This was the case in 70·1% of the patients with any mental disorder, in 71·4% of the cases with depressive disorders, in 75·0% of the cases with anxiety disorders and in 88·2% of the cases with any other mental disorders.

The average time span between the onset of DSM-IV mental disorders and the acromegaly diagnosis ranged between 9·4 and 22·4 years (mean of difference in years).

Any depressive disorder was diagnosed 13·6 ± 9·6 years before acromegaly was diagnosed. Dysthymia and MDE (significantly more often diagnosed in acromegalic patients) were diagnosed

Table 3. Affective disorders stratified by gender

Male	Acromegalic patients ($N = 38$)		Controls with chronic somatic disorders ($N = 1368$)		Controls without chronic somatic disorders ($N = 302$)		Acromegalic patients *vs.* controls with chronic somatic disorders			Acromegalic patients *vs.* controls without chronic somatic disorders		
	N	%	*N*	%	*N*	%	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Lifetime												
Any affective	9	23·7	225	14·5	35	9·8	1·87	0·86–4·08	0·113	**3·38**	1·3–8·6	**0·011**
Any MDE (incl GMC)	7	18·4	186	12·2	30	8·1	1·65	0·71–3·88	0·246	**3·08**	1·1–8·2	**0·025**
MDE	5	13·2	155	10·1	28	7·7	1·43	0·54–3·79	0·473	2·11	0·7–6·3	0·18
MDE (GMC)	2	5·3	31	2·1	2	0·5	2·17	0·46–10·37	0·33	**17·56**	3·3–94·5	**0·001**
Dysthymia	5	13·2	68	3·9	5	1·7	**3·78**	1·40–10·18	**0·009**	**8·70**	1·9–40·8	**0·006**
12 month												
Any affective	7	18·4	143	9·4	15	4·3	2·34	0·99–5·53	0·052	**4·63**	1·5–14·4	**0·008**
Any MDE (incl GMC)	5	13·2	104	7·0	11	2·9	2·15	0·80–5·74	0·128	**4·41**	1·3–15·0	**0·018**
MDE	3	7·9	93	6·4	10	2·7	1·41	0·41–4·78	0·586	2·37	0·6–9·9	0·235
MDE (GMC)	2	5·3	11	0·7	1	0·2	**6·25**	1·08–36·01	**0·04**	**46·54**	5·7–380·4	**0·000**
Dysthymia	5	13·2	68	3·9	4	1·4	**3·78**	1·40–10·18	**0·009**	**10·43**	2·0–53·8	**0·005**
Female	$N = 43$		$N = 1913$		$N = 128$							
Lifetime												
Any affective	19	44·2	564	27·4	21	14·7	**2·01**	1·07–3·77	0·03	**5·96**	2·0–17·6	**0·001**
Any MDE (incl GMC)	16	37·2	513	25·0	20	14·1	1·70	0·89–3·24	0·109	**4·46**	1·5–13·5	**0·008**
MDE	10	23·3	463	22·5	19	13·6	0·99	0·48–2·07	0·983	2·19	0·7–7·1	0·191
MDE (GMC)	6	14·0	50	2·5	1	0·6	**6·38**	2·40–16·92	0·000	**45·56**	4·3–485	**0·002**
Dysthymia	8	18·6	137	6·4	2	1·0	**2·69**	1·16–6·23	0·021	**26·30**	3·3–210	**0·002**
12 month												
Any affective	10	23·3	342	16·7	9	6·6	1·38	0·66–2·90	0·398	**5·22**	1·4–19·2	**0·013**
Any MDE (incl GMC)	7	16·3	286	13·9	8	6·0	1·10	0·48–2·57	0·817	3·45	0·9–13·0	0·067
MDE	3	7·0	251	12·2	8	6·0	0·49	0·15–1·65	0·251	1·38	0·3–7·1	0·697
MDE (GMC)	4	9·3	35	1·8	0	0·0	**5·62**	1·79–17·67	**0·003**	NA	NA	NA
Dysthymia	8	18·6	137	6·4	2	1·0	**2·69**	1·16–6·23	**0·021**	**26·30**	3·3–210	**0·002**

In bold: significant results ($P < 0·05$).

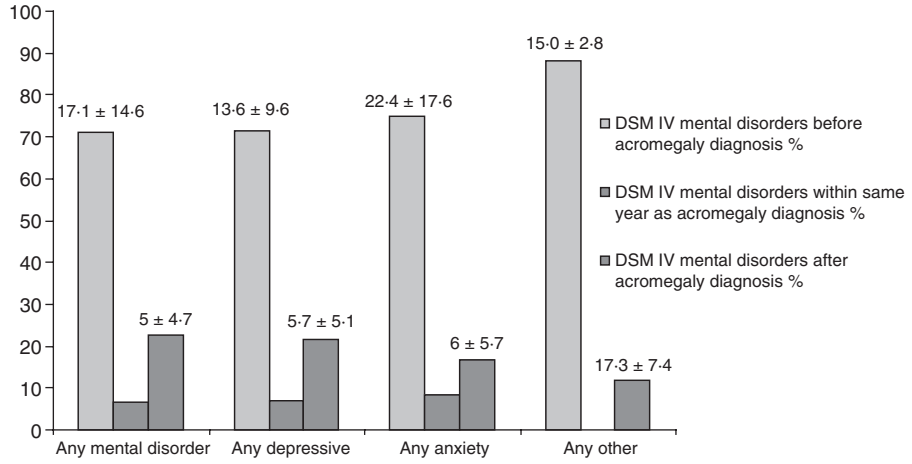

Fig. 1 Percentages of DSM-IV mental disorder diagnoses before, within the same year (±1 year) and after the acromegaly diagnosis in 81 acromegalic patients are reported. Numbers above bars indicate mean time (±SD) in years of first onset of disorder in relation to the diagnosis of acromegaly.

9·4 ± 9·1 years and 10·3 ± 7·1 years before the acromegaly diagnosis, respectively. Anxiety was diagnosed 22·4 ± 17·6 years before acromegaly.

For DSM-IV mental disorders that were first diagnosed after the acromegaly diagnosis (in 22·6% of the cases), the mean of differences between the two diagnoses was 5 ± 4·7 years.

Subgroup analysis within the acromegalic group

We also explored whether clinical characteristics such as acromegalic symptoms, comorbidities or treatment regimes of acromegalic patients with and without mental disorders differ (Table 4).

We found no significant differences between the DSM-IV mental disorder prevalence in patients with biochemically controlled or uncontrolled acromegaly, with or without macroadenomas, with or without surgery within the same year or with or without diabetes mellitus, arthralgia or pituitary deficiency.

However, the diagnoses of DSM-IV mental disorders in acromegalic patients were positively associated with radiotherapy at any time point of the treatment algorithm (OR = 4·5, 95% CI 1·4–14·2, $P = 0·011$) and current medical therapy (OR = 4·7, 95% CI 1·5–14·7, $P = 0·008$), probably as an indicator for a more severe disease status (patients who were not cured after surgery alone, but required additional treatment) rather than indicating a direct relationship.

Additionally, acromegalic symptoms such as tiredness, paraesthesia and hidrosis were associated with DSM-IV mental disorders.

Discussion

By using both a control group with mixed chronic disorders and a control group without chronic somatic disorders, we aimed at discriminating between the more specific effects of acromegaly and the general impact of chronic disease on mental health outcomes.

The key findings of our study are: (i) among acromegalic patients, there is a substantially increased prevalence of affective disorders, particularly major depression and dysthymia. The prevalence rates exceed the rates observed in representative samples of adults with and without chronic somatic disorders. (ii) Compared to somatically healthy subjects, the differences were even more pronounced. (iii) It is noteworthy, that the risk increase is limited to depressive syndromes; anxiety disorders such as panic attacks or panic disorders were found to be absent in the acromegalic patient sample, or the rates were overall comparable to a healthy population. (iv) In most cases, the DSM-IV mental disorder diagnoses were likely to be present before the acromegaly diagnosis. For the increased rate of affective disorders such as dysthymia and MDE, the mean time lapse between onsets suggests an overlap with the putative period of the already present overproduction of GH and IGF-1. (v) Radiotherapy as part of the treatment regimen in acromegaly, but not biochemical control, was a predictor for an increased risk for DSM-IV mental disorders.

Based on the comparison between acromegalics and patients with other somatic illnesses, our results indicate that most likely only a smaller part of the increased psychiatric morbidity in acromegalic patients is related to 'unspecific' effects ('such as

Table 4. Subgroup analysis within the acromegalic patient group comparing DSM-IV mental disorders between groups with different clinical characteristics

	Acromegalic patients without current DSM-IV mental disorder (Group 1)		Acromegalic patients with current DSM-IV mental disorder (Group 2)		Group 1 *vs.* Group 2		
	$N = 57$	%	$N = 24$	%	OR	95% CI	*P*-value
Clinical characteristics							
Macroadenomas	36	63·2	18	75·0	1·6	0·5–4·7	NS
Biochemically controlled	34	59·7	13	54·2	0·8	0·3–2·2	NS
Therapy							
Surgery in same year	4	7·0	3	12·5	1·7	0·3–8·8	NS
Surgery at any time	52	91·2	22	91·6	0·8	0·13–4·7	NS
Radiotherapy	10	17·5	10	41·7	4·5	1·4–14·2	**0·011**
Currently under medication	25	43·9	17	70·8	4·7	1·5–14·7	**0·008**
Currently under dopaminagonists	6	10·5	4	16·7	1·7	0·4–7·1	ns
Currently under somatostatin analogues	5	8·8	8	33·3	6·5	1·7–24·4	**0·006**
Currently under pegvisomant	4	7·0	6	25	10·0	1·9–52·7	**0·006**
Surgery, radiotherapy and medical therapy	9	15·8	9	37·5	4·4	1·3–14·4	**0·015**
Comorbidities							
Diabetes mellitus currently	3	37·5	3	50	4·6	0·2–119·6	NS
Arthralgia currently	22	78·6	7	70	0·3	0·0–2·8	NS
Pituitary deficiency	20	35·1	5	20·8	0·6	0·2–1·8	NS
Carpal tunnel syndrome	3	21·4	2	20	1·1	0·1–12·7	NS
Symptoms							
Acromegalic growth	6	10·5	6	25	3·2	0·9–12·1	**0·083**
Tiredness	22	38·6	20	83·3	8·7	2·4–31·0	**0·001**
Headache	14	24·6	12	50	2·9	1·0–8·5	**0·045**
Paraesthesia	22	38·6	18	75	5·5	1·8–16·7	**0·003**
Hidrosis	15	26·3	15	62·5	4·3	1·5–11·9	**0·006**
Visual disturbances	11	19·3	9	37·5	2·5	0·8–7·6	NS

In bold: significant results ($P < 0·05$).

demoralization') mediated by the general burden of chronical illness. The degree of excess psychiatric morbidity seems to be specific for and attributable to acromegaly and/or the central or systemic effect of GH and IGF-1 excess. This is indirectly supported by the fact that the patients themselves attribute the onset and recurrence of depressive syndromes to the illness and its complications.

Our results are in line with previous reports on unsystematic clinical observations in acromegalic patients. Bleuler, Blickenstorfer and Furman stated that acromegaly is accompanied by alterations of the mental state including mood changes, apathy and depressive symptoms.[3–6,12]

However, in small-scale studies aiming at quantifying and qualifying these alterations, numbers vary. Richert *et al.* report a percentage of psychopathological symptoms as high as 64·5% (20 out of 31) in preoperatively interviewed acromegalic patients.[8] On the contrary, Abed and colleagues found that only 10 out of 51 (19·6%) acromegalic patients fulfilled the criteria for possible psychiatric disorders based on the General Health Questionnaire score.[10] This discrepancy may be explained by different evaluation techniques, heterogeneous populations and small sample sizes.

Therefore, we aimed at recruiting a high number of patients and control subjects using a highly reliable evaluation technique (standardized computer-based personal interview).

Theoretically, various factors might explain our reported findings.

The direct or indirect effects of a pituitary lesion *per se* might influence the limbic system or prefrontal cortex with subsequent alterations of mood, behavioural control or personality.[28] However, we did not see an overall shifted risk profile for mental disorders in a mixed group of patients with different pituitary adenomas (hormonally active and inactive) in an earlier study of our group.[14] Additionally, we did not observe any differences between DSM-IV mental disorder rates in acromegalic patients with macro- or microadenomas, or patients with or without pituitary deficiencies in this study.

Despite the fact that this cross-sectional study has also not detected a relation between biochemical control and the prevalence of affective disorders, this particular aspect should be further addressed and evaluated in future prospective studies.

From epidemiological studies, it is known that diseases such as diabetes mellitus, heart diseases and chronic medical illness are risk factors for depression.[29,30] The systemic and chronic exposure to GH and IGF-1 in acromegalic patients leads to a whole range of comorbidities such as diabetes mellitus, sleep apnoea and arthralgia. Depressive symptoms might accompany the development of these conditions. However, the prevalence of depressive symptoms in the acromegalics cannot be explained by the presence of comorbid conditions such as diabetes or cardiovascular diseases alone, since the increased prevalence persisted even when these patients were compared to a control group with these comorbidities.

In a radiological study, we found distinct disturbances of the macroscopic brain tissue architecture in 44 acromegalic patients.[31] Compared to controls, grey matter and white matter volumes were enlarged at the expense of the cerebrospinal fluid. To date, we do not know how these alterations relate to clinical symptoms and brain function. However, it is conceivable that the altered brain morphology exposes acromegalic patients to a higher susceptibility for affective diseases. On the contrary, these changes might well explain reduced rates of other mental disorders such as panic. To date, we have no pathophysiological explanation for the reduced rate of panic disorders or attacks in the acromegalic patient group compared to subjects with chronic somatic disorders. We could speculate that a dysregulation of the hypothalamic–pituitary axis, or an altered neurosteroid secretion pattern might shift the threshold for panic attacks or the sensitivity to contextual clues in acromegalic patients.[32,33]

Even though the effect of the acromegaly diagnosis as a life event does not seem to play a major role as a trigger for DSM-IV mental disorders, some 'post-diagnostic conditions' still account for differences in mental health between acromegalic subgroups. The fact that patients under medical treatment were at a higher risk of comorbid psychiatric diseases most probably reflects the fraction with a persistent disease. However, biochemical control as mentioned above was not a discriminating factor in contrast to radiotherapy, which confirms results by other authors investigating quality of life in acromegalic patients.[34,35] When we additionally analysed mental disorders in patients with and without radiotherapy or radiotherapy as a covariate in the logistic regression, the higher rates of mental disorders, however, persisted.

A limitation for the interpretation of our study results is the cross-sectional data collection. It relies on the recall ability and willingness of patients and controls. This recall ability might be biased by many factors. For instance, a distinct personality pattern of acromegalic patients has been previously discussed. This could be a reason for a different reporting pattern.[3–7,36]

The control group was examined years earlier than the acromegalic patient group and temporal alterations of social psychopathology patterns as a potential bias must be taken into account. However, high test–retest reliability and validity of the DIA-X/M-CIDI interviews have been previously reported.[37]

Additionally, we cannot exclude that acromegalic patients who did not participate might differ in some respects from the examined patients. A preferential participation of 'unhealthy' or 'healthy' patients might have introduced a selection bias (response rate of 56%). However, the main reasons for nonparticipation were distance to study centre, and unwillingness to spend time and effort on the examinations. Due to these reasons, we do not believe that the nonparticipating group was significantly different from the examined group regarding mental health and therefore should not significantly change the outcome.

Between patients treated at the Max-Planck Institute of Psychiatry and the Department of Internal Medicine of the Ludwig-Maximilians-University Munich, we observed significant differences in age distribution (mean age 55 *vs.* 44·7 years, respectively) and civil state (55·8% *vs.* 73·6% patients were married, respectively). Rates of DSM-IV mental disorder between patients treated at the Max-Planck Institute of Psychiatry and the Department of Internal Medicine of the Ludwig-Maximilians-University Munich did not differ except for the prevalence of anxiety disorders (Max-Planck Institute patients *vs.* Ludwig-Maximilians-University patients: OR = 6·65, 95% CI 1·32–33·54). These differences might have occurred if patients with or without additional psychiatric

problems visited either centre. On the contrary, both centres treat most of the acromegalic patients in the region. Therefore, the sample and the overall DSM-IV mental disorder rates should be representative for an acromegalic population in Germany. However, in general the heterogeneous patient group limits the interpretation of our study, since certain aspects of acromegaly do not occur often enough in the patient group to allow for correlations and statistical comparisons that are desirable.

The DIA-X/M-CIDI instrument is specifically validated for subjects aged 18–65 years. To detect a potential measurement bias, we additionally performed all statistical analyses exclusively in the group of acromegalic patients and controls aged 18–65 years. All significant odds ratios became even more extreme compared to the odds in control groups. Our approach should therefore deliver very conservative rates.

Conclusion and perspective

Acromegalic patients might be at risk of suffering from a specific psychopathological risk profile. Affective disorders are primarily present in this patient group. The DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Version) morbidity might accompany the phase of GH/IGF-1 excess and could be regarded as an additional acromegalic symptom.

Psychopathological symptoms may be altered by different treatment modalities such as radiation. Undiagnosed and untreated affective disorders could be a cause for the frequently reported reduced quality of life in some acromegalic patients. Therefore, specific psychiatric diagnostics and therapy might improve treatment results.

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