Clinical characteristics of pain in patients with pituitary adenomas

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Abstract

Objective: Clinical presentation of pituitary adenomas frequently involves pain, particularly headache, due to structural and functional properties of the tumour. Our aim was to investigate the clinical characteristics of pain in a large cohort of patients with pituitary disease.

Design: In a cross-sectional study, we assessed 278 patients with pituitary disease ($n=81$ acromegaly; $n=45$ Cushing's disease; $n=92$ prolactinoma; $n=60$ non-functioning pituitary adenoma).

Methods: Pain was studied using validated questionnaires to screen for nociceptive vs neuropathic pain components (painDETECT), determine pain severity, quality, duration and location (German pain questionnaire) and to assess the impact of pain on disability (migraine disability assessment, MIDAS) and quality of life (QoL).

Results: We recorded a high prevalence of bodily pain ($n=180$, 65%) and headache ($n=178$, 64%); adrenocorticotrophic adenomas were most frequently associated with pain ($n=34$, 76%). Headache was equally frequent in patients with macro- and microadenomas (68 vs 60%; $P=0.266$). According to painDETECT, the majority of the patients had a nociceptive pain component ($n=193$, 80%). Despite high prevalence of headache, 72% reported little or no headache-related disability (MIDAS). Modifiable factors including tumour size, genetic predisposition, previous surgery, irradiation or medical therapy did not have significant impact neither on neuropathic pain components (painDETECT) nor on headache-related disability (MIDAS). Neuropathic pain and pain-related disability correlated significantly with depression and impaired QoL.

Conclusions: Pain appears to be a frequent problem in pituitary disease. The data suggest that pain should be integrated in the diagnostic and therapeutic work-up of patients with pituitary disease in order to treat them appropriately and improve their QoL.

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Introduction

The clinical presentation of pituitary adenomas such as acromegaly, Cushing's disease (CD), prolactinomas and non-functioning pituitary adenomas (NFPA) involves pain, particularly headache, in more than one-third of all patients, probably due to both structural and functional properties of the tumour (1). Mechanical, biochemical, vascular and biopsychosocial aspects, and

also a genetic predisposition for primary headache might be involved in the pathogenesis of headache in pituitary disease (1). Among functional pituitary tumours, growth hormone (GH)-secreting adenomas and prolactinomas have been specifically associated with headache, possibly mediated by the change in endocrine status rather than the pituitary mass *per se* (2). Transsphenoidal surgery may

lead to significant improvement in headache in patients with non-secreting and hypersecretory pituitary microadenomas (3).

Besides one study on headache in patients with pituitary adenomas (4), systematic studies on pain in patients with pituitary adenomas are still lacking. In acromegaly, GH excess leads to persisting joint-related complaints such as arthropathy and arthralgia (5). On the other hand, both animal models and clinical studies have documented hypothalamo–pituitary–adrenal axis dysfunction as a potential contributing factor to the development of chronic pain via stress mechanisms, allowing potential association with a hypercortisolaemic state in CD (6). However, this has not been systemically investigated so far.

Several studies have documented the frequent comorbidity of depression and impaired quality of life (QoL) in patients suffering from chronic pain. Bair *et al.* (7) demonstrated more severe pain, greater disability, and poorer health-related QoL in patients with chronic pain suffering from depression and anxiety. The association between neuropsychiatric comorbidities and pituitary disease is well established. Patients with CD are frequently affected by major psychiatric disorders such as depression, anxiety and psychosis, even after long-term biochemical cure of the disease (8, 9). Besides, there is an increased prevalence of affective disorders or anxiety-associated personality traits in patients with acromegaly and prolactinomas (10, 11). Interestingly, patients with NFPA exhibited a comparable personality pattern, potentially as a result of the pituitary lesion and/or associated hormonal dysregulations (12).

Furthermore, impaired QoL is a common finding in patients with pituitary adenomas (13). In acromegaly, decreased QoL seems to persist despite long-term cure of GH excess (14). In CD, biochemical remission does not prevent the patients from experiencing a considerable decrease in QoL with physical and psychosocial impairments, especially in the presence of hypopituitarism (15). Female patients with microprolactinomas present with impaired QoL, mostly due to anxiety and depression, while impaired QoL inversely correlates with prolactin (PRL) levels (16, 17).

The aim of this study was to describe the clinical characteristics of pain including the following aspects: primary site of perceived pain, quality of pain, nociceptive vs neuropathic pain components, side shift, severity/intensity, frequency and duration, other associated symptoms, trigger factors of pain, family history in relationship with pain as well as pain-alleviating factors

in patients with pituitary adenomas and how these might be influenced by modifiable factors such as tumour and treatment characteristics. We also assessed the role of pain on disability and QoL.

Subjects and methods

Patients

In this cross-sectional study, we assessed 278 patients with pituitary adenoma ($n=206$ from the Max Planck Institute of Psychiatry and $n=72$ from the Ludwig Maximilians University) referred to our endocrinological specialty clinics between 1990 and 2012: 81 patients with acromegaly, 45 patients with CD, 92 patients with prolactinoma and 60 patients with NFPA. The study was approved by the local ethical committee, and all subjects gave their written informed consent.

The study was conducted on average 10 ± 1 years after surgery for acromegaly, and 11 ± 7 and 13 ± 8 years after initial diagnosis of prolactinoma and NFPA respectively. Mean time after CD remission was 7 ± 3 years.

Assessment of pain

‘German pain questionnaire’ ► The ‘Germanpainquestionnaire version 1’ (GPQ), developed by the German Chapter of the International Association for the Study of Pain, comprises demographic data, phenotypic characteristics, associated symptoms, affective and sensory qualities of pain, pain-relieving and -intensifying factors, previous pain treatment, pain-related disability, a depression scale (CES-D), comorbidities, social factors and health-related QoL (SF-36) (18).

painDETECT ► The reliability of the painDETECT questionnaire, developed as a screening tool to identify neuropathic pain components, has been confirmed in several studies (19, 20). Following cut-offs have been suggested for screening purposes: score ≤ 12 (neuropathic component unlikely) and ≥ 19 (neuropathic component likely); score 13–18 (uncertain, neuropathic pain component possible).

Migraine disability assessment ► The migraine disability assessment (MIDAS) questionnaire was designed to quantify headache-related disability over the past 3 months (21) (sum of missed work, school, household chores or non-work activity days, where productivity was reduced by $\geq 50\%$). Headache-related disability can be classified

into 'little or no disability' (Grade I), 'mild disability' (Grade II), 'moderate disability' (Grade III) and 'severe disability' (Grade IV).

Assessment of QoL

EQ-5D (EQ visual analogue scale) ► The EuroQOL (EQ-5D) questionnaire, developed from the EuroQoL group, is a standardised health-related QoL instrument. It consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and the EQ visual analogue scale (EQ-VAS). Each dimension has three levels (no problems, some problems, extreme problems) (22).

Assessment of depression

Beck Depression Inventory ► The Beck Depression Inventory (BDI) is one of the most widely used instruments for measuring severity of depression (23). It comprises 21 questions with at least four possible answer choices about how the patient has been feeling in the last week. A total score of 0–9 indicates minimal, a score of 10–18 mild, a score of 19–29 moderate and a score of 30–63 severe depression (24).

Assessment of comorbidities, biochemical variables and tumour characteristics

Clinical characteristics were assessed via interview, physical examination and laboratory analyses. Tumour characteristics were determined by thin-section magnetic resonance imaging (2 mm) of the pituitary. Visual field defects were confirmed by Goldmann perimetry. Details on treatment history, comorbidities, past medical history and actual symptoms were collected from patients' charts. Patients were treated according to the consensus treatment guidelines for the respective pituitary disease.

Biochemical control of acromegaly was defined as: (i) GH below 1 µg/l during a 2-h glucose tolerance test and (ii) insulin-like growth factor1 (IGF1) within two s.d.s of an age- and gender-adjusted normative range (25). Biochemical control of CD was defined as (i) urinary free cortisol values within the assay-specific normal range and (ii) serum cortisol ≤ 1.8 g/dl (50 nmol/l) after 1 mg dexamethasone (26). Normoprolactinaemia was defined as PRL of ≤ 25 ng/ml for women and ≤ 20 ng/ml for men.

Evaluation of pituitary function comprised basal fasting measurements of IGF1, thyrotrophin, free thyroxine, total triiodothyronine, gonadotropins, PRL and

testosterone (in men) or oestradiol (in women) and an insulin tolerance test, in the case of suspected corticotroph or somatotroph pituitary deficiency.

Medical treatment

Use of analgesics comprised non-steroidal anti-inflammatory agents (19%) and opioid analgesics (5%). Dopamine agonists were applied due to pituitary disease in 123 cases. Patients with secondary hypoadrenalism, hypothyroidism, hypogonadism and hyposomatotropism were studied while on optimised replacement therapy. Antidepressant therapy was not recorded.

Statistical analyses

Statistical analysis was performed using PASW Statistics (formerly SPSS) Version 18 for Windows. Sample characteristics were compared using χ^2 tests and ANOVA. Differences in pain characteristics between patients with different forms of pituitary disease were evaluated with an analysis of covariance (ANCOVA) controlling for age, gender, BMI and tumour size, characteristics that differed between the four groups. In the case of group differences, *post hoc* tests, corrected for multiple comparisons following the Bonferroni–Holm procedure, were applied. Correlation of pain with QoL and depression in the whole group of patients with pituitary adenomas and within the subgroups was performed using Pearson's correlation coefficient. A *P* value of <0.05 was considered statistically significant.

Results

Patient demographics

Of the 278 pituitary adenoma patients included, 170 were female (61%) and 108 were male (39%). Mean age was 53 ± 13 years, mean BMI was 27 ± 6 kg/m². Overall, 180 patients (65%) complained of any kind of pain. Adrenocorticotrophin-secreting pituitary adenomas were most frequently associated with pain ($n=34$, 76%), followed by GH-secreting pituitary adenomas ($n=59$, 73%).

Tumour characteristics

For the whole group, 163 of the tumours were macroadenomas (59%) and 87 were microadenomas (31%). In 28 patients (10%), no data were available on tumour size. Macroadenomas were more common in the NFPA (83%)

and acromegaly groups (65%), while microadenomas were more frequent in the CD (67%) and prolactinoma groups (51%; $P=0.000$). Headache was equally frequent in patients with macroadenomas and patients with microadenomas (68 vs 60%; $P=0.266$).

Treatment characteristics

One hundred and eighty-two patients (66%) underwent transsphenoidal adenomectomy: these patients were not affected more frequently by headache (64 vs 62%; $P=0.787$). Fifty-one patients (18%) underwent additional radiotherapy ($n=19$, stereotactic fractionated; $n=13$, gammaknife; $n=1$, cyberknife; $n=18$, unknown). Overall, 162 (58%) patients received ≥ 1 medical therapy, comprising somatostatin analogues ($n=50$), dopamine agonists ($n=123$), the GH receptor antagonist ($n=9$) and adrenergic compounds ($n=15$). Demographic, tumour and treatment characteristics as well as comorbidities of the overall study population and according to each tumour subtype are given in Table 1.

Pain characteristics according to GPQ

Primary pain site ► For the whole group, the most common pain location was the lower back (67%), followed by the neck (66%) and the shoulder/arm/hand regions (66%). Table 2 provides an overview of the primary sites of pain in the different pituitary disorders.

Side shift ► The majority of the pituitary adenoma patients reported no pain side shift (91%). No side shift was recorded in 98% of CD, 95% of prolactinoma, 88% of acromegaly and 85% of NFPA patients respectively ($P=0.028$).

Quality ► The commonest quality of pain was described as 'deep' ($n=180$, 65%). 'Deep' pain was reported by 62% of acromegaly, 80% of CD, 64% of prolactinoma and 58% of NFPA patients ($P>0.05$).

Intensity ► Regarding pain intensity within the last 4 weeks, pituitary adenoma patients reported on a scale of 0 (=no pain) to 10 (=most severe pain) a mean pain intensity of 4 ± 2 , the most severe pain intensity as 6 ± 2 and the mildest pain intensity as 2 ± 2 . CD patients reported the most severe pain intensity with 7 ± 2 , whereas prolactinoma patients reported the mildest pain intensity with 2 ± 2 .

Frequency and duration ► The majority of the overall study population (41%) complained of episodic pain, while 21% complained of permanent pain. Permanent pain was most frequent in CD patients (31%). Only 10% of the patients described their pain as chronic with pain attacks. Median pain duration was 14 ± 10 years. Pain side shift, quality, intensity and frequency amongst tumour subtypes are presented in Table 2.

Associated features

The commonest associated symptoms comprised visual disturbances (28%), noise sensitivity (19%), nausea (19%) and photophobia (18%). Indeed, pain was accompanied by visual disturbances in 25, 27 and 28% of the acromegaly, prolactinoma and NFPA patients respectively, whereas CD patients most frequently associated pain to photophobia (29%). Fifteen percent of the photophobic CD patients suffered neither from headache nor from pain of the neck region.

Trigger factors

Physical stress appeared to trigger pain in 41% of the pituitary adenoma patients, followed by emotional stress (21%) and other causes (16%).

Alleviating factors

Non-pharmacological alleviating factors included 'resting' (44%) and the use of motion/exercise (25%).

Family history

The majority of the pituitary adenoma patients (86%) had no family history of a pain disorder (acromegaly, 83%; CD, 84%; prolactinoma, 84%, NFPA, 93%) ($P>0.05$). Pain associated features, trigger factors, alleviating factors and family history within the study population are given in Table 3.

Headache-related disability (according to MIDAS)

According to MIDAS, the majority of the patients (72%) presented with little or no headache-related disability (Grade I) on daily life. Within the subgroups, 73% of the acromegalic, 63% of the CD, 72% of the prolactinoma and 70% of the NFPA subjects had little or no headache-related disability. However, 25% of the CD population reported severe headache-related disability (Grade IV). Distribution of MIDAS scores in the overall study population and according to each tumour subtype is shown in Fig. 1.

Table 1 Patient demographics, tumour characteristics, treatment and comorbidities. Significant effects are in bold face.

Patient demographics	All patients	Acromegaly (1)	CD (2)	Prolacti- noma (3)	NFPA (4)	Statistical analyses		Post-hoc tests ^a , P values					
						ANOVA		1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
						Global test	P value						
<i>n</i>	278	81	45	92	60								
Sex <i>n</i> (%)													
Male	108 (38.8)	38 (46.9)	8 (17.8)	23 (25)	39 (65)	35.33	0.000						
Female	170 (61.2)	43 (53.1)	37 (82.2)	69 (75)	21 (35)			0.004	NS	NS	NS	0.000	0.000
Age mean (s.d.)	52.8 (13.2)	55.5 (11.8)	46.2 (11.1)	49.2 (13.8)	60.2 (10.6)								
BMI mean (s.d.)	27.31 (6.26)	29.02 (5.24)	26.25 (1.06)	25.73 (6.96)	28.27 (4.96)								
Tumour characteristics <i>n</i> (%)													
Macroadenoma	163 (58.6)	53 (65)	15 (33.3)	45 (48.9)	50 (83)	57.58	0.000	0.000	0.000	NS	NS	0.000	0.000
Microadenoma	87 (31.3)	6 (7)	30 (66.7)	47 (51.1)	4 (7)								
No data available	28 (10.1)	22 (28)	0 (0)	0 (0)	6 (10)								
Biochemical control <i>n</i> (%)	142 (65.1)	49 (60.5)	33 (73.3)	60 (65.2)	NA (NA)	2.1	0.350						
Treatment <i>n</i> (%)													
Surgery	182 (65.5)	73 (90.1)	44 (97.8)	13 (14.8)	52 (86.7)	177.85	0.000	NS	0.000	NS	0.000	NS	0.000
Radiotherapy	51 (18.3)	20 (24.7)	14 (31.1)	2 (2.3)	15 (25.0)	23.79	0.000	NS	0.001	NS	0.001	NS	0.001
Medical therapy	162 (58.3)	60 (74.1)	15 (33.3)	87 (94.5)	0 (0.0)	283.41	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Comorbidities <i>n</i> (%)													
Diabetes mellitus	43 (15.5)	22 (27.2)	11 (24.4)	4 (4.7)	6 (10.0)	18.32	0.000	NS	0.000	0.028	NS	NS	NS
Pituitary deficiency	147 (52.9)	48 (59.3)	32 (71.1)	22 (24.4)	45 (75.0)	66.1	0.000	NS	0.000	0.004	0.000	NS	0.000
Corticotrope	109 (39.2)	37 (45.7)	24 (53.3)	13 (14.9)	35 (58.3)	55.4	0.000	NS	0.000	0.020	0.000	NS	0.000
Thyrotrope	85 (30.6)	24 (29.6)	20 (44.4)	7 (8.0)	34 (56.7)	57.8	0.000	NS	0.003	0.000	0.000	NS	0.000
Gonadotrope	90 (32.4)	36 (44.4)	9 (20.0)	15 (17.0)	30 (50.0)	27.86	0.000	NS	0.001	NS	NS	0.023	0.000
Somatotrope	57 (20.5)	2 (2.5)	14 (31.1)	7 (8.1)	34 (56.7)	87.11	0.000	0.000	NS	0.000	0.000	0.000	0.000

CD, Cushing's disease; NFPA, non-functioning pituitary adenoma; NS, not significant; NA, not applicable.

^aCorrected for multiple comparisons.

Table 2 Pain side shift, primary pain site, pain intensity, quality of pain and pain frequency. Significant effects are in bold face.

						Statistical analyses			Post-hoc tests ^b , P values						
						Global test	ANCOVA ^a								
						χ ²	P value	F	P value	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4

CD, Cushing's disease; NFPA, non-functioning pituitary adenoma; ANCOVA, analysis of covariance; NS, not significant.

^aCorrected for age, sex, BMI and tumour type.^bCorrected for multiple comparisons.

Table 3 Pain-associated features, trigger factors, alleviating factors and family history. Significant effects are in bold face.

	All patients		Acromegaly (1)		CD (2)		Prolactinoma (3)		NFPA (4)		Global test		Post-hoc tests (corrected for multiple comparisons, P-values)					
	n	%	n	%	n	%	n	%	n	%	χ^2	P-value	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
Associated features																		
Nausea	52	18.7	14	17.2	11	24.4	10	10.9	7	11.7	21.44	0.011	NS	NS	NS	NS	NS	NS
Vomiting	21	7.6	7	8.6	5	11.1	7	7.6	2	3.3	14.99	NS						
Photophobia	50	18.0	9	11.1	13	28.9	20	21.7	8	13.3	14.98	NS						
Noise sensitivity	53	19.0	12	14.8	17	37.8	17	18.5	7	11.7	21.23	0.012	NS	NS	NS	NS	NS	NS
Visual disturbances	77	27.7	20	24.7	15	33.3	25	27.2	17	28.3	33.03	0.000	NS	NS	NS	NS	NS	NS
Oedema/erythema	43	15.5	13	16.0	11	24.5	10	10.9	9	15.0	28.88	0.001	NS	NS	NS	NS	NS	NS
Hypersensitivity of the skin	30	10.8	12	14.8	11	24.5	15	16.3	11	18.4	27.42	0.001	NS	NS	NS	NS	NS	NS
Triggers/causes																		
Disease	79	28.4	27	33.3	25	55.6	15	16.3	12	20.0	20.71	0.000	NS	0.044	NS	0.000	0.003	NS
Surgery	44	15.8	14	17.3	12	26.7	8	8.7	10	16.7	5.52	NS						
Physical stress	114	41.0	30	37.0	25	55.6	36	39.1	23	38.3	4.23	NS						
Emotional stress	57	20.5	14	17.3	13	28.9	25	27.2	5	8.3	1.76	NS						
Other cause	45	16.2	12	14.8	10	22.2	13	14.1	10	16.7	10.39	0.015	NS	NS	NS	NS	NS	0.013
No cause	23	8.3	6	7.4	1	2.2	8	8.7	8	13.3	3.44	NS						
Accident	13	4.7	5	6.2	0	0	6	6.5	2	3.3	0.55	NS						
Hereditary	14	5.0	5	6.2	1	2.2	3	3.3	5	8.3	5.83	NS						
Alleviating factors																		
Non-pharmacologic																		
Physical stress	5	1.8	1	1.2	1	2.2	3	3.3	0	0.0	5.22	NS						
One-sided posture	7	2.5	4	4.9	1	2.2	2	2.2	0	0.0	8.13	NS						
Motion/exercise	70	25.2	25	30.9	17	37.8	17	18.5	11	18.3	7.76	NS						
Rest	122	43.9	40	49.4	26	57.8	37	40.2	19	31.7	17.08	NS						
Family history																		
Positive	40	14.4	14	17.3	7	15.6	15	16.3	4	6.7	3.43	NS						

CD, Cushing's disease; NFPA, non-functioning pituitary adenoma; NS, not significant.

Figure 1

Distribution of migraine disability assessment (MIDAS) scores amongst tumour types and for the group as a whole.

The highest MIDAS scores were recorded in the CD and NFPA patient group (20 ± 40 and 12 ± 38 respectively). The mean MIDAS score for the whole group was 12 ± 33 days.

Neuropathic vs nociceptive pain (according to painDETECT)

The majority of the patients fulfilled screening criteria for a nociceptive pain component (80%), followed by uncertain pain (11%) and a neuropathic pain component (1%). Within the subgroups, 84% of the acromegalic, 78% of the CD, 72% of the prolactinoma and 88% of the NFPA subjects complained of nociceptive pain (Fig. 2).

The highest mean painDETECT scores were seen in the prolactinoma and CD patient group (9 ± 8 and 8 ± 7 respectively). Mean painDETECT score for the whole group was 7 ± 7 .

Impact of modifiable factors

Patients with hormonal hypersecretion independent of tumour type differed significantly from patients with biochemically controlled pituitary disease regarding the painDETECT score ($P=0.007$). Other modifiable factors including tumour size, genetic predisposition, previous surgery, irradiation or medical therapy did not have a significant impact on headache-related disability (MIDAS score) or neuropathic pain components (painDETECT score; data not shown).

Correlation with depression and QoL

Table 4 shows the Pearson's r correlation coefficients between neuropathic pain components (painDETECT) and headache-related disability (MIDAS) with depression

(BDI) and health-related QoL (visual analogue scale EQ-VAS) in all 278 patients and within the subgroups.

There was statistical significance in all correlations between neuropathic pain, depression and impaired health-related QoL ($P<0.05$). Regarding headache-related disability, there was again statistical significance in nearly all correlations with depression, with the exception of acromegalic ($P=0.412$) and prolactinoma patients ($P=0.315$) and with health-related QoL with the exception of NFPA patients ($P=0.127$).

Discussion

The aim of this study was to investigate the clinical characteristics of pain in pituitary disease. To our knowledge, this is the first study to examine bodily pain and headache in a large cohort of patients with pituitary adenomas.

The main findings of our study are as follows: i) there is a high prevalence of bodily pain in patients with pituitary adenomas independent of the tumour type; ii) patients with CD seem to be especially susceptible to pain, compared with the other patient groups; iii) the majority of the pituitary patients suffer from a nociceptive pain component; (iv) we recorded a high incidence of headache independent of tumour type; however, the majority of the study population reported little or no headache-related disability in everyday life; (v) modifiable factors including tumour size, genetic predisposition, previous surgery, irradiation or medical therapy do not seem to have a significant impact on pain; and (vi) pain and pain-related disability correlated significantly with depression and impaired QoL.

Figure 2

Distribution of painDETECT scores amongst tumour types and for the group as a whole.

Table 4 Correlation of pain with quality of life (QoL) and depression. Significant effects are in bold face.

	BDI		EQ-VAS	
	<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value
painDETECT				
Total	0.431	0.000	−0.415	0.000
Acromegaly	0.318	0.011	−0.342	0.007
Cushing's disease	0.719	0.000	−0.577	0.000
Prolactinoma	0.528	0.000	−0.479	0.000
NFPA	0.327	0.011	−0.283	0.031
MIDAS				
Total	0.290	0.009	−0.412	0.000
Acromegaly	0.109	NS	−0.451	0.000
Cushing's disease	0.420	0.007	−0.347	0.030
Prolactinoma	0.126	NS	−0.265	0.036
NFPA	0.460	0.001	−0.216	NS

BDI, Beck Depression Inventory; EQ-VAS, EQ visual analogue scale of the EuroQOL questionnaire; MIDAS, migraine disability assessment; *r*, Pearson's correlation coefficient; NFPA, non-functioning pituitary adenoma; NS, not significant.

Patients with pituitary adenomas suffer frequently from bodily pain; however, the causal connection between bodily pain and pituitary disease is not clear. For acromegaly, we know that persistent GH excess can lead to arthropathy and arthralgia (5). On the other hand, PRL has been involved in the development of pain disorders via modulation of the transient receptor potential vanilloid type 1 (27). Notably, NFPA patients lacking hormone excess presented a comparable pain profile as patients with other pituitary entities, underlying the importance of the pituitary mass *per se*.

We found that CD patients are more prone to develop pain, which is not surprising, since hypothalamo–pituitary–adrenal axis dysfunction has been suggested as a contributing factor to the development of chronic pain both in animal models and clinical studies (6). Recent studies have identified cortisol as a positive predictor of pain sensitivity (28). Cortisol levels correlate negatively with pain thresholds during stress (29), potentially explaining the high incidence of pain in CD.

According to painDETECT, patients with pituitary disease are affected by nociceptive rather than neuropathic pain components. As nociceptive pain is caused by stimulation of peripheral nerve fibres that respond to stimuli approaching or exceeding the intensity threshold of nociceptors, musculo-skeletal abnormalities and/or a state of low-grade chronic inflammation in hormone excess syndromes e.g. CD might play a role in pain pathogenesis in these patients. However, this finding needs to be considered with caution, as no physician-based confirmation of neuropathic vs nociceptive pain

was obtained in our study and the painDETECT questionnaire has been designed for screening rather than definite diagnosis (30). Moreover, the finding of more nociceptive than neuropathic pain is somewhat contradictory to previous results on pain mechanisms in patients with pituitary adenomas (polyneuropathy and compression neuropathies due to median nerve oedema in acromegaly (31) and peripheral neuropathies due to high incidence of diabetes mellitus in CD (32)).

Regarding the incidence of headache in our study, these results fall at the higher end of published rates for patients with pituitary adenomas so far (38–70%) (1). Initially, we attributed this finding to the high ratio of macroadenomas in our group: however, this could not be confirmed by further analysis. Mechanical/compressive explanations in the pathogenesis of headache are not supported in the literature and the association between tumour size and headache remains unclear (33). Interestingly, headache did not induce significant disability in everyday life of most patients, probably because of its episodic nature. The average MIDAS score for the whole group was 12, indicating moderate disability and comparing to scores as high as 96 being reported e.g. in refractory migraine (34). In general, headache-related disability appeared to be somewhat lower in functional than non-functional pituitary disease.

The effect of local/mechanical modifiable factors such as tumour size, previous surgery and irradiation or systemic factors, e.g. genetic predisposition, hormonal hypersecretion and medical therapy, was previously investigated only regarding its relationship with headache in patients with pituitary adenomas. Regarding bodily pain, we anticipated a lacking influence of local/mechanical factors on examined pain features. Nonetheless, neither systemic parameters such as medical therapy and hormonal hypersecretion (significant effect only on painDETECT score) had significant impact on pain, suggesting previous irreversible effects on the CNS leading to chronic pain. This contradicts previous findings, especially in patients with prolactinoma and acromegaly, showing positive correlation between headache and circulating PRL levels or GH excess respectively (35, 36).

Finally, we showed that pain and pain-related disability correlated with depression and impaired QoL. As depression is treatable and the relation between pain and depression is likely bi-directional, treatment of depressive symptoms may likely improve the overall QoL of affected patients.

As a weakness of this study we have to consider, next to its cross-sectional design, the fact that there was no

register-based age- and gender-matched control group, which could account for pain and headache suffering in a matched population. However, as the aim of the study was to emphasise the possible role of hormonal hypersecretion in patients with pituitary adenomas, we contrasted with a clinical control group of patients with NFPA, instead of normal population controls. We believe that this study design is justifiable and should be sufficient to give a reliable picture of pain characteristics in patients with pituitary adenomas.

Picking up the pain problem is relatively straight forward when a cautious history is taken and when one specifically addresses pain as a potential symptom. Whether this is performed by using structured questionnaires (e.g. current study) or in a less structured way is of minor importance, as long as pain is not neglected. In a proportion of patients, a referral to specialist pain assessment and treatment (e.g. by orthopedic surgeons, anesthesiologists, neurologists) may be useful, but this needs to be determined on a case-by-case basis, and no general recommendations can be given in our view. The other way around, pain specialists should be alert for pituitary tumours when looking for secondary headache causes mimicking, e.g. cluster headache, and express promptly clinical suspicion of a pituitary adenoma in respective headache or pain patients.

Conclusions

Pain appears to be a significant problem in pituitary disease associated with a range of pain phenotypes. Pain syndromes seem to persist even after long-term biochemical cure of the pituitary disease. As a clinical recommendation, we believe that the assessment of pain should be integrated in the diagnostic work-up and follow-up of patients with pituitary disease. In this context, the interrelation between pain and affective symptoms should also be taken into account.

Regarding treatment, affected patients can be difficult to treat. The best strategy is certainly to identify patients with symptoms suggestive of pituitary adenoma early and treat them causally. This may prevent or slow the development of pain symptoms, at least in a subgroup of patients (e.g. arthropathy and arthralgia in acromegaly). Once the pain problem has fully developed, multimodal treatment strategies are often necessary (optimisation of endocrinological treatment, pharmaceutical pain management, physiotherapy, behavioural psychotherapy when appropriate etc.).

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