High prevalence of fibromyalgia-associated symptoms in patients with hypothalamic-pituitary disorders

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ABSTRACT

Objectives. *Various complaints of patients with fibromyalgia often resemble clinical features observed in patients with hypothalamic-pituitary diseases. The aim of this study was to evaluate whether patients with hypothalamic-pituitary diseases are at increased risk for fibromyalgia syndrome (FMS).*

Methods. *A questionnaire for evaluating fibromyalgia-associated symptoms was sent to 121 patients with hypothalamic-pituitary disorders (HPD) (60 women, 61 men; mean age, 55.4 years; range, 21–83 years) of the endocrine outpatient clinic. 115 patients (57 women, 58 men; mean age 56.9 years; range, 21 to 82 years) with cardiovascular diseases (CD) served as controls.*

Results. *Fibromyalgia-associated symptoms regarding muscular complaints were significantly more frequent in the HPD group than in CD patients (53.7 % vs. 35.7%, p= 0.003). In particular, we found a significant higher prevalence of autonomic symptoms in the HPD group as compared to the CD group regarding several qualities (cold hands, p=0.039; flatulence, p=0.022; tiredness, p=0.017). In addition, swollen and painful finger joints were reported more often in the HPD group than in the CD group (p=0.002). Of note, no differences regarding any fibromyalgia-associated symptom were detected when patients with hypothalamic-pituitary hormone excess syndromes were compared to those with a pituitary pathology without hormonal excess. Similarly, prevalence of fibromyalgia-associated symptoms was not related to the treatment modality of pituitary disease; i.e. surgical vs. conservative or any hormonal replacement therapy.*

Conclusion. *Our data suggest that patients with hypothalamic-pituitary disorders may be at increased risk of developing fibromyalgia-associated symptoms.*

Introduction

Musculoskeletal pain is a frequent complaint of patients with hypothalamic-pituitary diseases. In addition, patients often suffer from fatigue, exhaustion, and sleep disturbances. Interestingly, these symptoms are similar to those seen in fibromyalgia syndrome (FMS), while some of the clinical features of FMS resemble those described in adrenal insufficiency or growth hormone deficiency (1-3). On the contrary, excess production of pituitary hormones due to pituitary tumours can also be associated with rheumatological symptoms (4).

According to the criteria of the American College of Rheumatology, fibromyalgia can be classified as a form of rheumatism that is associated with widespread muscle pain in combination with tenderness at least 11 or more of 18 specific tender points (5). The widespread muscle pain must be present for at least 3 months. Usually patients show additional autonomic or functional symptoms such as fatigue, sleep disturbances, depressions and physical deconditioning (6, 7), without any objective findings on physical examination or laboratory and imaging modalities (8-10). The 2010 ACR preliminary classification criteria diagnoses fibromyalgia as the sum of widespread pain index (WPI) and total symptom severity (SS) with continuing symptoms for more than 3 months and no hint of other disorders that would otherwise explain the pain (11). The SS scale score is the sum of the severity of the 3 symptoms (fatigue, unrefreshed sleep, cognitive symptoms) and the number of somatic symptoms. The estimated prevalence of FMS in the general population is relatively high with 2% to 4% of the population affected (12, 13). Females are at greater risk with a female-to-male ratio of approximately 9:1, especially through middle-age (9, 14).

In FMS, abnormalities of the hypothalamic-pituitary (HP) axis have been

reported. A substantial number of patients with FMS have low levels of insulin-like growth factor (IGF-1) and growth hormone (GH), suggesting dysregulation of the GH/IGF-1 axis (1, 2, 15). Since no consistent defects in pituitary function have been found and most patients show normal pituitary responsiveness to exogenously administered growth hormone releasing hormone (GHRH) (1, 2), the reported dysregulation is most likely of hypothalamic origin (1, 6). Moreover, several studies revealed lower levels of basal plasma cortisol (16-18) and a diminished expression of glucocorticoid receptors in patients with FMS compared to controls (16) or a disturbed receptor function (19). Another study demonstrated a lower total cortisol release in response to the Trier Social Stress Test and exogenous ACTH stimulation, but normal salivary free cortisol concentrations and ACTH levels when compared to healthy controls (20). In the study of Calis *et al*., 95% of the patients with FMS had a lower 11-deoxycortisol level after metyrapone than the lowest 11-deoxycortisol level after metyrapone detected in healthy controls (21). Finally, it has been previously shown in a population-based prospective cohort study that subjects with high levels of cortisol post-dexamethasone, indicating a failure to suppress the HPA axis, and low cortisol levels in morning saliva and high levels in evening saliva, which indicates a disruption of the diurnal rhythm, were at increased risk of new-onset chronic widespread pain (22). These data also point to an alteration of the hypothalamic-pituitary-adrenal axis.

In addition, FMS patients were found to have elevated basal values of FSH and LH as well as lowered basal values of estrogens and free triiodothyronine (FT3) (23, 24). It is still unclear whether the observed HP axis abnormalities predispose patients to develop FMS, or whether the chronic nature of FMS symptoms alter the HP axis activity (25). The aim of the present study was to evaluate whether and to which extent patients with various hypothalamic-pituitary disorders suffer from symptoms associated with the FMS.

Table I. Pituitary pathologies in the hypothalamic-pituitary disorders (HPD) group.

Pathology	Number of patients	Percentage
Prolactinoma	31	25.6
Non-functioning pituitary adenoma (NFPA)	66	54.5
Hypopituitarism of unknown origin	1	0.8
ACTHoma	4	3.3
STHoma	2	1.7
TSHoma	1	0.8
Craniopharyngeoma	8	6.6
Sheehan-syndrome	1	0.8
Central diabetes insipidus of unknown origin	2	1.7
Meningeoma	2	1.7
Suprasellar tumour	1	0.8
Intrasellar cyst	1	0.8
FSHoma	1	0.8
Total	121	100.0

Materials and methods

A questionnaire, developed for evaluating skeletal, muscular, vegetative symptoms, and swollen joints in FMS, was sent to 121 patients with hypothalamic-pituitary disorders (HPD; 60 women, 61 men; mean age, 55.4 years; range, 21–83 years) of the endocrine out-patients clinic. The questionnaire was based on the FMS questionnaire by the German Fibromyalgia Association DFV (26). Baseline characteristics of the study participants in the HPD group (Table I) were as follows: 68.6% (n=83) suffered from a non-functioning pituitary adenoma or other pituitary pathology without hormonal excess, whereas 31.4 % were treated for a hormone producing pituitary adenoma (n=38). Moreover, 67.8 % of the patients had prior surgery for their endocrine disease (n=82). All patients with impaired hypothalamic-pituitary function received adequate hormone replacement therapy (n=71, 58.7%).

As control group, 115 patients (57 women, 58 men; mean age 56.9 years; range, 21–82 years) with cardiac disease (CD) such as coronary heart disease, pulmonary hypertension, chronic heart failure, cardiac valve disease, cardiomyopathy, hypertensive cardiac disease and arrhythmias, were included in the study.

The questionnaire addressed various autonomic symptoms, including complaints of cold hands, dry mouth, sweating, sleep disturbances, nocturnal teeth grinding, flatulence, obstipation and diarrhoea, dysphagia, dyspnoea, cardiac arrythmias, dysaesthesia, dysuria, headache, and tiredness. In addition, patients were asked if they suffered from chronic back pain or depression.

The study protocol was approved by the Ethics Committee of the University of Kiel, Germany, informed consent was obtained.

Statistical analysis

Data are expressed as mean±standard deviation or as median where appropriate. Results obtained in the two groups were compared using the non-parametric Wilcoxon signed-ranks test. A *p*-value of less than 0.05 was considered significant.

Results

Specific musculoskeletal symptoms are significantly more common in patients with hypothalamic-pituitary disorders

Fibromyalgia-associated symptoms regarding muscular complaints were significantly more frequent in the HPD group than in CD patients (p=0.003; Fig. 1). In particular, patients in the HPD group suffered significantly more from muscular pain of the neck (p=0.001), forearms (p=0.046), calves (p=0.015) and thighs (p=0.004; data not shown). Although there were no significant differences between the two groups regarding skeletal symptoms in total (p=0.181, Fig. 1), significant differences were noted regarding shoulder (p=0.007), elbow (p=0.038) and finger pain (p=0.001; data not shown). In addition, swollen and painful finger joints were more common in the HPD than in the CD group (p=0.002; data not shown). In contrast, no significant

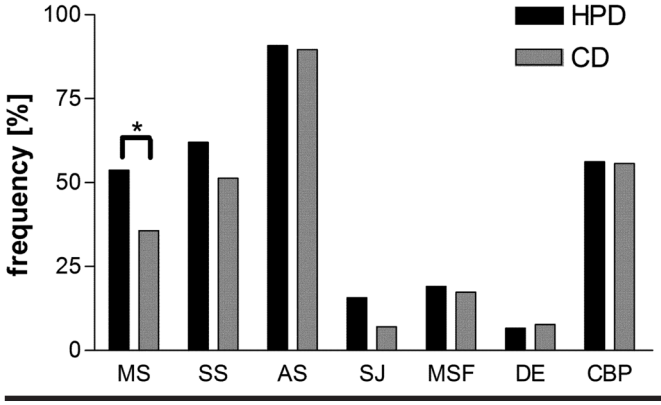

Fig. 1. Fibromyalgia-associated symptoms in HPD patients (black columns) and CD patients (grey columns). MS: muscular symptoms; SS: skeletal symptoms; AS: autonomic symptoms; SJ: swollen joints; MSF: morning stiffness; DE: depression; CBP: chronic back pain; *p<0.05.

Table II. Autonomic symptoms in patients with hypothalamic-pituitary disorders (HPD) and cardiovascular disease (CD). Significant differences are depicted as bold p-values.

Symptom	HPD (n= 121)	CD (n=115)	p-value
Cold hands	51.2%	37.4%	**0.039**
Dry mouth	32.2%	27.0%	0.386
Sweating	38.0%	28.7%	0.109
Sleep disturbances	47.1%	36.5%	0.152
Teeth grinding	16.5%	13.0%	0.398
Flatulence	38.8%	24.3%	**0.022**
Obstipation	17.4%	11.3%	0.194
Diarrhoea	13.2%	13.9%	0.853
Dysphagia	16.5%	13.0%	0.317
Dyspnoe	14.9%	22.6%	0.139
Cardiac arrhythmia	23.1%	39.1%	**0.007**
Dysaesthesia	32.2%	21.7%	0.093
Dysuria	5.0%	0.9%	0.059
Headache	35.5%	27%	0.217
Tiredness	61.2%	43.5%	**0.017**

Table III. Fibromyalgia-associated symptoms in hypothalamic-pituitary disorder (HPD) patients, subclassified according to hormonal activity, treatment modality and hormonal replacement therapy.

HPD (n=121)		MS	SS	AS	SJ	MSF	DE	CBP
Hormonal activity	yes (n=38)	47.4%	68.4%	92.1%	10.5%	10.5%	2.6%	57.9%
	no (n=83)	56.6%	59.0%	90.4%	18.1%	22.9%	8.4%	55.4%
	p-value	0.683	0.683	0.655	0.366	0.132	0.317	1.000
Treatment modality	surg (n=82)	51.2%	61.0%	89.0%	14.6%	15.9%	3.7%	52.4%
	cons (n=39)	59.0%	64.1%	94.9%	17.9%	25.6%	12.8%	64.1%
	p-value	0.796	0.405	1.000	1.000	0.405	0.102	0.491
Hormonal replacement therapy	yes (n=64)	53.1%	59.4%	92.2%	17.2%	20.3%	6.3%	53.1%
	no (n=57)	54.4%	64.9%	89.5%	14.0%	17.5%	7.0%	59.6%
	p-value	1.000	0.602	0.527	0.593	0.637	0.705	0.564

MS: muscular symptoms; SS: skeletal symptoms; AS: autonomic symptoms; SJ: swollen joints; MSF:morning stiffness; DE: depression; CBP: chronic back pain; surg: surgical; cons: conservative.

difference with respect to total swollen joints (p=0.061) or morning stiffness (p=0.857; Fig. 1) emerged. While there were no significant differences between the two groups regarding chronic back pain (Fig. 1), patients in the HPD group complained significantly more often of pain of the cervical spine (24.0% *vs*. 12.2%; p=0.033).

Patients with hypothalamic-pituitary disorders suffer more from cold hands, flatulence and tiredness, but not depression

With respect to autonomic symptoms in total no significant differences were found between the HPD and the CD group (p=0.827; Fig. 1). However, some specific autonomic symptoms were more prevalent in the HPD group (Table II). In particular, patients in the HPD group suffered significantly more often from cold hands (p=0.039), flatulence (p=0.022) and tiredness (p=0.017). Prevalence of depression did not differ between both groups (Fig. 1).

Hormonal activity or treatment modality in patients with hypothalamic-pituitary disorders do not affect prevalence of fibromyalgia-associated symptoms

Comparison of patients with hypothalamic-pituitary hormone excess syndromes with those having non-secretory adenomas and with other pituitary pathologies without hormonal excess did not reveal any differences regarding fibromyalgia-associated symptoms (Table III). Similarly, prevalence of fibromyalgia-associated symptoms was not associated with the treatment modality of pituitary disease; *i.e*. surgical *vs*. conservative or to any hormonal replacement therapy (Table III).

GH deficiency is associated with specific complaints

No relationship was observed between a specific pituitary hormone deficiency and the prevalence of fibromyalgia symptoms in total (Table IV). However, in the HPD group patients with GH deficiency suffered significantly more from dysaesthesia (40.0% *vs*. 28.4%; p=0.052) when compared to patients with adequate GH secretion, whereas ACTH deficiency was significantly associated with less sweating (24.5% *vs*. 47.2 %; p=0.028).

Skeletal symptoms and swollen joints are more common in female than male patients with hypothalamic-pituitary disorders

In the HPD group 72.1% of the females suffered from skeletal symptoms whereas male patients showed significantly less symptoms (50.8%; p=0.006). In addition, females more often reported swollen joints (21.7% *vs*. 9.8%; p=0.046). However, there were no significant differences between males and females with respect to muscular and autonomic symptoms, depres-

Table IV. Hypothalamic-pituitary disorders (HPD) and the prevalence of fibromyalgia-associated symptoms.

HPD (n=121)		MS	SS	AS	SJ	MSF	DE	CBP
LH, FSH	yes (n=62)	51.6%	61.3%	93.5%	17.7%	21.0%	4.8%	54.8%
	no (n=59)	55.9%	62.7%	88.1%	13.6%	16.9%	8.5%	57.6%
	p-value	0.862	0.739	0.257	0.617	0.655	0.414	0.847
GH	yes (n=40)	52.5%	60.0%	87.5%	15.0%	20.0%	5.0%	42.5%
	no (n=81)	54.3%	63.0%	92.6%	16.0%	18.5%	7.4%	63.0%
	p-value	0.835	1.000	1.000	1.000	0.317	0.655	0.144
ACTH	yes (n=49)	51.0%	57.1%	89.8%	16.3%	16.3%	6.1%	46.9%
	no (n=72)	55.6%	65.3%	91.7%	15.3%	20.8%	6.9%	62.5%
	p-value	0.853	0.564	0.763	0.796	0.808	1.000	0.178
TSH	yes (n=48)	45.8%	58.3%	89.6%	14.6%	18.8%	6.3%	47.9%
	no (n=73)	58.9%	64.4%	91.8%	16.4%	19.2%	6.8%	61.6%
	p-value	0.336	0.683	0.763	1.000	0.782	1.000	0.180
ADH	yes (n=13)	53.8%	61.5%	92.3%	15.4%	15.4%	7.7%	61.5%
	no (n=108)	53.7%	62.0%	90.7%	15.7%	19.4%	6.5%	55.6%
	p-value	0.527	0.705	1.000	0.655	0.564	0.317	0.157

MS: muscular symptoms; SS: skeletal symptoms; AS: autonomic symptoms; SJ: swollen joints; MSF: morning stiffness; DE: depression; CBP: chronic back pain; LH: luteinizing hormone; FSH: follicle-stimulating hormone; GH: growth hormone; ACTH: adrenocorticotropic hormone; TSH: thyroid stimulating hormone; ADH: antidiuretic hormone.

sion, morning stiffness, and chronic back pain (data not shown).

Discussion

FMS is a painful syndrome of non-articular origin, characterised by widespread musculoskeletal pain and symptoms such as fatigue, sleep disturbances, gastrointestinal complaints and psychological problems that are similar to those experienced by patients with hormone deficiencies. Hypothalamic-pituitary disorders, therefore, might be associated with fibromyalgia-like symptoms, the extent of which is not completely known. Of note, the aetiology of this diffuse complex of clinical symptoms is not yet completely understood. The data presented herein demonstrate that patients with hypothalamic-pituitary diseases suffer significantly more often from muscular symptoms in comparison to a control group without a history of hypothalamic-pituitary disease. Similarly, there was a higher prevalence of several autonomic symptoms and we found a significant difference between the HPD and the CD group regarding painful shoulders, elbows, fingers, swollen finger joints and pain of the cervical spine.

Our data support the hypothesis that hypothalamic-pituitary disorders and FMS may both represent a state of endocrine dysfunction, the nature of which remains to be elucidated. Investigations in the aetiology of FMS have focused upon central pain processing systems (27). Presumably, patients with FMS develop functional changes in the central nervous system with excitability of neurons, enlargement of their receptive fields, reduction in pain threshold, and recruitment of novel afferent inputs (9). It has been shown that fibromyalgia patients have deficiencies in serotonergic, dopaminergic and noradrenergic neurotransmission (28, 29). The enhanced pain perception may also be due to increases in pro-nociceptive neurotransmitters like glutamate and substance P (29, 30). Further risk factors for FMS or enhanced pain responses include genetic factors, environmental triggers, and abnormal neuroendocrine and autonomic nervous system function (22, 31, 32). Disturbances of the hypothalamic-pituitary-adrenal axis could also be important in the pathophysiology of FMS. Symptoms may be due to low circulating cortisol, alterations in central neurotransmitter systems or disturbance of the relationship between cortisol and central neurotransmitter function (33). The reduced hormonal and autonomic responses appear to reflect impairment in the hypothalamic or central nervous system response to stimuli rather than a primary defect at the level of the pituitary gland or the peripheral glands (34). Recent data suggest a putative role of cytokines in the pathogenesis of FMS (35). Finally, brain imaging studies show structural differences between patients with FMS and healthy individuals (28, 36). Presumably, a combination of multiple, impaired functions in different systems may lead to profound physiologic and clinical consequences in FMS.

Since the lack of cortisol or growth hormone can clinically manifest as muscular weakness or tiredness, it is conceivable that the reported symptoms in the HPD group are due to cortisol or growth hormone deficiency. In fact, many patients with FMS have low levels of IGF-1 and GH and/or cortisol. However, in our study we could not demonstrate any relationship to either a particular hormone deficiency or to hormonal replacement therapy. Only dysaesthesia correlated with a hormone deficiency. Furthermore, it should be considered that patients with any pituitary pathology (and no secretory deficiency) frequently complain about sleep disturbances and tiredness (37, 38).

The frequent occurrence of fibromyalgia-like symptoms in the HPD group cannot either be explained by the chronic character of the pituitary diseases per se, because this applies also to the control group. Due to the tight functional connection between the sympathico-adrenal and the hypothalamic-pituitary-adrenal gland system (39, 40), a functional impairment of the adrenal medulla has been demonstrated in patients with primary as well as secondary adrenal insufficiency (41, 42). The expression of phenylethanolamine N-methyltransferase (PNMT), the key enzyme for the conversion of noradrenaline to adrenaline, is induced by glucocorticoids (43, 44). It was shown in rats and mice that activation of PNMT in the periphery is dependent on maintenance of physiological levels of glucocorticoids (45-47). Therefore, adrenomedullary function might be adversely affected by prolonged periods of hypocortisolism. Moreover, patients with hypothalamic pituitary disorders often harbour morphological abnormalities on magnetic resonance imaging, the importance of which for FMS has

not yet been clarified. As the occurrence of fibromyalgia symptoms in the HPD group was to a large extent independent of any hormone deficiency, disturbances in central neurotransmitters may be a contributory factor for development of the clinical symptoms.

Conclusion

In summary, our results indicate that patients with hypothalamic-pituitary disorders may be at increased risk of developing fibromyalgia-associated symptoms. Rheumatologists should consider such endocrine disorders in patients evaluated for FMS. It remains to be clarified though whether fibromyalgia-like symptoms in the HPD group reflect pre-existing vulnerability to FMS, or rather represent central changes promoting the occurrence of FMS.

References

1. LEAL-CERRO A, POVEDANO J, ASTORGA R *et al*.: The growth hormone (GH)-releasing hormone GH-insulin-like growth factor-1 axis in patients with fibromyalgia syndrome. *J Clin Endocrinol Metab* 1999; 84: 3378-81.
2. YUEN KC, BENNETT RM, HRYCIW CA, COOK MB, RHOADS SA, COOK DM: Is further evaluation for growth hormone (GH) deficiency necessary in fibromyalgia patients with low serum insulin-like growth factor (IGF)-1 levels? *Growth Horm IGF Res* 2007; 17: 82-8.
3. GEENEN R, JACOBS JW, BIJLSMA JW: Evaluation and management of endocrine dysfunction in fibromyalgia. *Rheum Dis Clin North Am* 2002; 28: 389-404.
4. STAVROU S, KLEINBERG DL: Rheumatic manifestations of pituitary tumors. *Curr Rheumatol Rep* 2001; 3: 459-63.
5. WOLFE F, SMYTHE HA, YUNUS MB *et al*.: The American College of Rheumatology 1990. Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; 33: 160-72.
6. JONES KD, DEODHAR P, LORENTZEN A, BENNETT RM, DEODHAR AA: Growth hormone perturbations in fibromyalgia: a review. *Semin Arthritis Rheum* 2007; 36: 357-79.
7. KAPOOR SR, HIDER SL, BROWNFIELD A, MATTEY DL, PACKHAM JC: Fibromyalgia in patients with rheumatoid arthritis: driven by depression or joint damage? *Clin Exp Rheumatol* 2011; 29: 88-91.
8. CONRAD I: Diagnosis and clinical signs of fibromyalgia. *Schmerz* 2003; 17: 464-74.
9. CHONG Y-Y, NG B-Y: Clinical Aspects and Mangement of Fibromy algia Syndrome. *Ann Acad Med Singapore* 2009; 38: 967-73.
10. MEENAGH G, SAKELLARIOU G, IAGNOCCO A *et al*.: Ultrasound imaging for the rheumatologist XXXIX. Sonographic assessment of the hip in fibromyalgia patients. *Clin Exp Rheumatol* 2012; 30: 319-21.
11. WOLFE F, CLAUW DJ, FITZCHARLES MA *et al*.: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* (Hoboken) 2010; 62: 600-10.
12. WOLFE F, ROSS K, ANDERSON J, RUSSELL IJ, HERBERT L: The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995; 38: 19-28.
13. LAWRENCE RC, FELSON DT, HELMICK CG, ARNOLD LM, CHOI H, DEYO R: Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008; 58: 26-35.
14. WHITE KP, HARTH M: Classification, epidemiology, and natural history of fibromyalgia. *Curr Pain Headache Rep* 2001; 5: 320-9.
15. BENNETT R: Growth hormone in musculoskeletal pain states. *Curr Pain Headache Rep* 2005; 9: 331-8.
16. MACEDO JA, HESSE J, TURNER JD, MEYER J, HELLHAMMER DH, MULLER CP: Glucocorticoid sensitivity in fibromyalgia patients: decreased expression of corticosteroid receptors and glucocorticoid-induced leucine zipper. *Psychoneuroendocrinology* 2008; 33: 799-809.
17. GUR A, CEVIK R, NAS K, COLPAN L, SARAC S: Cortisol and hypothalamic-pituitary-gonadal axis hormones in follicular-phase women with fibromyalgia and chronic fatigue syndrome and effect of depressive symptoms on these hormones. *Arthritis Res Ther* 2004; 6: R 232-8.
18. RIVA R, MORK PJ, WESTGAARD RH, RØ M, LUNDBERG U: Fibromyalgia syndrome is associated with hypocortisolism. *Int J Behav Med* 2010; 17: 223-33.
19. GEISS A, ROHLEDER N, ANTON F: Evidence for an association between an enhanced reactivity of interleukin-6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia. *Psychoneuroendocrinology* 2012; 37: 671-84.
20. WINGENFELD K, HEIM C, SCHMIDT I, WAGNER D, MEINLSCHMIDT G, HELLHAMMER DH: HPA axis reactivity and lymphocyte glucocorticoid sensitivity in fibromyalgia syndrome and chronic pelvic pain. *Psychosom Med* 2008; 70: 65-72.
21. CALIS M, GÖKCE C, ATES F *et al*.: Investigation of the hypothalamic-pituitary-adrenal axis (HPA) by 1 microg ACTH test and metyrapone test in patients with primary fibromyalgia syndrome. *J Endocrinol Invest* 2004; 27: 42-6.
22. MCBETH J, SILMAN AJ, GUPTA A *et al*.: Moderation of psychosocial risk factors through dysfunction of the hypothalamic-pituitary-adrenal stress axis in the onset of chronic widespread musculoskeletal pain. *Arthritis Rheum* 2007; 56: 360-71.
23. NEECK G: Neuroendocrine and hormonal perturbations and relations to the serotonergic system in fibromyalgia patients. *Scand J Rheumatol* 2000; 113 (Suppl.): 8-12.
24. EL MAGHRAOUI A, TELLAL S, ACHEMLAL L *et al*.: Bone turnover and hormonal perturbations in patients with fibromyalgia. *Clin Exp Rheumatol* 2006; 24: 428-31.
25. CROFFORD LJ: The hypothalamic-pituitary-adrenal axis in the pathogenesis of rheumatic diseases. *Endocrinol Metab Clin North Am* 2002; 31: 1-13.
26. HÄUSER W, ZIMMER C, FELDE E, KÖLLNER V: [What are the key symptoms of fibromyalgia? Results of a survey of the German Fibromyalgia Association] (in German). *Schmerz* 2008; 22: 176-83.
27. STAUD R: Brain imaging in fibromyalgia syndrome: *Clin Exp Rheumatol* 2011; 29: 109-17.
28. SCHWEINHARDT P, SAURO KM, BUSHNELL MC: Fibromyalgia: a disorder of the brain? *Neuroscientist* 2008; 14: 415-21.
29. CLAUW DJ: Fibromyalgia: an overview. *Am J Med* 2009; 122: S3-S13.
30. SARZI-PUTTINI P, ATZENI F, CAZZOLA M: Neuroendocrine therapy of fibromyalgia syndrome: an update. *Ann N Y Acad Sci* 2010; 1193: 91-7.
31. BRADLEY LA: Pathophysiologic mechanisms of fibromyalgia and its related disorders. *J Clin Psychiatry* 2008; 69 (Suppl. 2): 6-13.
32. CASSISI G, SARZI-PUTTINI P, CAZZOLA M: Chronic widespread pain and fibromyalgia: could there be some relationships with infections and vaccinations? *Clin Exp Rheumatol* 2011; 29: 118-26.
33. PARKER AJ, WESSELY S, CLEARE AJ: The neuroendocrinology of chronic fatigue syndrome and fibromyalgia. *Psychol Med* 2001; 31: 1331-45.
34. ADLER GK, MANFREDSDOTTIR VF, CRESKOFF KW: Neuroendocrine abnormalities in fibromyalgia. *Curr Pain Headache Rep* 2002; 6: 289-98.
35. DI FRANCO M, IANNUCCELLI C, VALESINI G: Neuroendocrine immunology of fibro- myalgia. *Ann N Y Acad Sci* 2010; 1193: 84-90.
36. KIM SH, CHANG Y, KIM JH *et al*.: Insular cortex is a trait marker for pain processing in fibromyalgia syndrome-blood oxygenation level-dependent functional magnetic resonance imaging study in Korea. *Clin Exp Rheumatol* 2011; 29: 19-27.
37. GAPSTUR R, GROSS CR, NESS K: Factors associated with sleep-wake disturbances in child and adult survivors of pediatric brain tumors: a review. *Oncology Nursing Forum* 2009; 36: 723-31.
38. BAUMANN CR, WERTH E, STOCKER R, LUDWIG S, BASSETTI CL: Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study. *Brain* 2007; 130: 1873-1883.
39. KVETNANSKÝ R, PACÁK K, FUKUHARA K, CIZZA G, GOLDSTEIN DS, KOPIN IJ: Sympathoadrenal system in stress. Interaction with the hypothalamic-pituitary-adrenocortical system. *Ann N Y Acad Sci* 1995; 771: 131-58.
40. KVETNANSKY R, FUKUHARA K, PACAK K *et al*.: Endogenous glucocorticoids catecholamine synthesis and release at rest and during immobilization stress in rats. *Endocrinology* 1993; 133: 1411-9.
41. HARBECK B, KROPP P, MÖNIG H: Effects of short-term nocturnal cortisol replacement on cognitive function and quality of life in patients with primary or secondary adrenal insufficiency: a pilot study. *Appl Psychophysiol Biofeedback* 2009; 34: 113-9.

42. MERKE DP, BORNSTEIN SR: Congenital adrenal hyperplasia. *Lancet* 2005; 365: 2125-36.
43. WAN DC, LIVETT BG: Induction of phenylethanolamine N-methyltransferase mRNA expression by glucocorticoids in cultured bovine adrenal chromaffin cells. *Eur J Pharmacol* 1989; 172: 107-15.
44. WONG DL, TAI TC, WONG-FAULL DC, CLAYCOMB R, KVETNANSKY R: Genetic mechanisms for adrenergic control during stress. *Ann N Y Acad Sci* 2004; 1018: 387-97.
45. BOHN MC, GOLDSTEIN M, BLACK IB: Expression and development of phenylethanolamine-N-methyltransferase (PNMT) in rat brain stem: studies with glucocorticoids. *Dev Biol* 1986; 114: 180-93.
46. JEONG KH, JACOBSON L, PACÁK K, WIDMAIER EP, GOLDSTEIN DS, MAJZOUB JA: Impaired basal and restraint-induced epinephrine secretion in corticotropin-releasing hormone-deficient mice. *Endocrinology* 2000; 141: 1142-50.
47. KVETNANSKY R, KUBOVCAKOVA L, TILLINGER A, MICUTKOVA L, KRIZANOVA O, SABBAN EL: Gene expression of phenylethanolamine N-methyltransferase in corticotrophin-releasing hormone knockout mice during stress exposure. *Cell Mol Neurobiol* 2006; 26: 735-54.