CEREBROSPINAL FLUID BIOGENIC AMINE METABOLITES IN FIBROMYALGIA/FIBROSITIS SYNDROME AND RHEUMATOID ARTHRITIS

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Objective. **To compare the levels of biogenic amines in the cerebrospinal fluid (CSF) of primary fibromyalgia syndrome (PFS) patients with those in the CSF of controls.**

Methods. **Metabolites of serotonin, norepinephrine, and dopamine were identified in CSF, using high performance liquid chromatography with coulometric detection.**

Results. **CSF levels of metabolites from all 3 neurotransmitters were lower in PFS patients than in controls.**

Conclusion. **A low rate of turnover of several neurotransmitters supports the proposed hypothesis of a metabolic defect in PFS and suggests that the defect occurs at a neuroregulatory level.**

Primary fibromyalgia/fibrositis syndrome (PFS) is a chronic, painful musculoskeletal disorder commonly seen in rheumatology practice (1–4). The severity of discomfort experienced by PFS patients is comparable with that affecting rheumatoid arthritis (RA) patients (5,6). Even the ability of PFS patients to perform specific work tasks is often limited in a comparable manner to the impairment found in RA patients (6). PFS patients sleep poorly, exhibiting patterns of nonrestorative sleep that is relatively deficient in stage IV non–rapid eye movement and other parameters (7,8).

Light and electron microscopy studies of tender muscles have failed to identify any structural abnormality specific for PFS (9). The role of fibrous bands constricting muscle fibers, observed by phase-contrast microscopy (10), also remains unclear pending independent confirmation. Chemical analysis of muscle tissue from PFS patients has suggested an abnormality in high-energy phosphate metabolism (11,12), but the contribution of such a defect to the pain experienced by affected individuals is still uncertain.

An alternative explanation for the widespread pain is that there is aberrant perception of discomfort from relatively normal tissues. That concept is not new with regard to PFS (13), but it has been revived in new ways (14). Moldofsky and Warsh (15) suggested that patients with PFS may have a deficiency of serotonin, since that neurotransmitter affects both deep restorative sleep and pain perception. Serotonin is a recognized chemical mediator of deep sleep and of pain perception by both the thalamus and the peripheral nervous system (16). It is known to alter the function of substance P (17), particularly with reference to the interpretation of sensory stimuli.

Support for the serotonin deficiency hypothesis was found when it was observed that PFS patients had

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a higher density of serotonin reuptake receptors on their circulating platelets, and lower levels of serum serotonin, than did matched controls (18). Serum tryptophan levels (19) and transmembrane transport of tryptophan from serum (20) were also lower in patients with PFS.

The question remained, however, as to whether PFS patients would exhibit abnormalities in central nervous system (CNS) metabolism of serotonin. We have reported elevated levels of substance P (21), but normal levels of other oligopeptide neurotransmitters (22,23), in cerebrospinal fluid (CSF) from patients with PFS. In the present investigation, the same CSF samples used in those earlier studies were reexamined for their concentrations of biogenic amine neurotransmitters, in comparison with CSF from RA patients and healthy controls.

PATIENTS AND METHODS

Subjects. Seventeen female patients with PFS (1,21,22,24) (mean ± SD age 45.8 ± 3.0 years, range 20–61 years) and 12 control subjects (11 women, 1 man) without fibromyalgia (mean age 44.8 years, range 22–63 years) were enrolled by 2 of the authors (HV in Norway and FN in Sweden). Five of the controls (all women; mean age 61.8 years, range 55–72 years) had RA (25) without concomitant fibromyalgia (26). The RA patients all had atlantoaxial dislocation and underwent lumbar puncture to monitor the CSF flow. The other 7 controls were healthy, pain-free individuals (6 women, 1 man; mean age 32.6 years, range 22–37 years). After giving informed consent using a document approved by the local ethics committee, all subjects agreed to donate CSF obtained by lumbar puncture.

No patient or healthy control subject regularly took psychotropic drugs or opiates. Most of the PFS patients were infrequently taking paracetamol as an analgesic. One of the RA patients was receiving no medication; treatment of each of the other 4 RA patients, respectively, was as follows: azathioprine 100 mg/day + indomethacin 75 mg/day, auranofin 6 mg/day + methylprednisolone 7.5 mg/day, cyclosporine 3.0 mg/day + methylprednisolone 20 mg/day, and auranofin 6 mg/day + methylprednisolone 10 mg/day + ketoprofen 100 mg/day. All analgesic and sedative medications were discontinued 48 hours prior to lumbar puncture.

CSF sampling. Sixteen milliliters of CSF was collected from each subject by lumbar puncture using a 22-gauge needle (21). No subject experienced any serious adverse effect. None of the samples were bloodstained. The CSF was divided into 2-ml aliquots, which were immediately frozen in the dark at −70°C. Samples were transported, with solid CO_2, by plane to San Antonio, where they were again stored at −70°C until thawed for analysis.

Laboratory studies. All biologic assays were conducted on numbered samples, by a technician who was blinded to their source. The substances measured were 5-hydroxyindole acetic acid (5-HIAA; the product of serotonin metabolism), 3-methoxy-4-hydroxyphenethylene glycol (MHPG) from norepinephrine, and homovanillic acid (HVA) from dopamine. Identification of these biogenic amine metabolites and their quantitation in CSF were performed as previously described (27), with minor modifications.

Briefly, 1 ml of acetonitrile was added to 100 μl of CSF to precipitate protein. The mixture was vortexed, then centrifuged at 16,000*g* for 10 minutes at 0–4°C. One milliliter was withdrawn and dried to residue under a nitrogen stream. The residue was redissolved in 100 μl of mobile phase and injected into a high performance liquid chromatography column for analysis. The mobile phase contained 50 m*M* phosphoric acid and 225 μ*M* 1-octane sulfonic acid, adjusted to pH 2.55 with NaOH. The flow rate was 1.5 ml/minute through 2 Regis "Little Champ" 0.46 × 5-cm columns (Spherisorb packing, 3μ; Bodman Chemicals, Aston, PA).

Coulometric detection was accomplished with 2 electrochemical cells in series (Coulochem 5100A; ESA, Bedford, MA) with a voltage of 0.18V in detector 1 (D1) and 0.37V in detector 2 (D2). System Gold software (Beckman, Fullerton, CA) was used to integrate peak areas. The concentration of each metabolite was determined by comparison of sample peak areas with extracted standard peak areas for MHPG, 5-HIAA, and HVA. Final concentrations were then calculated relative to identically extracted internal standards of known concentration.

Statistical analysis. The SPSS statistical software system was used for all analyses. CSF biogenic amine concentrations for PFS patients were compared with those in the combined control groups (RA patients and healthy subjects) by unpaired 2-tailed *t*-tests. Nonparametric comparisons (Wilcoxon), performed because of non-normal distributions of the 3 biogenic amines, gave comparable values. Correlations among the PFS CSF concentrations of each of the biogenic amine metabolites measured in the present study, and other components previously measured in the same CSF (21–23), were computed using Pearson's pairwise 2-tailed test.

RESULTS

A summary of the demographic characteristics of the subjects is shown in Table 1. The mean age of the PFS group was nearly the same as that of the 2 control groups combined (non-PFS group), but it should be noted that the mean age in the RA control group and that in the healthy control group were quite disparate.

Table 2 shows that the mean CSF concentration of each metabolite was lower for the PFS patients than for the non-PFS group. The difference was significant for MHPG ($P = 0.028$) and HVA ($P = 0.005$), but only approached significance for 5-HIAA ($P = 0.057$). Also shown in Table 2 are values for the RA control group and the healthy control group separately. The mean MHPG concentrations in the RA group and the healthy control group were quite similar, and were

Table 1. Demographic characteristics of the study participants*

Characteristic	PFS patients (n = 17)	Control groups		
		Non-PFS (n = 12)	RA (n = 5)	NC (n = 7)
Age (years)	45.9 ± 2.1	44.8 ± 3.0	61.8 ± 3.0	32.6 ± 1.8
No. females/no. males	17/40	11/1	5/0	6/1
Morning stiffness (minutes)	33.5 ± 20.8	NA	39.0 ± 13.4	0
Pain duration (years)	13.4 ± 1.7	NA	22.2 ± 4.9	NA
ESR (mm/hour)	6.2 ± 0.7	NA	40.8 ± 17.7	ND

* Except for no. females/no. males, values are the mean ± SEM. PFS = primary fibromyalgia/fibrositis syndrome; Non-PFS = rheumatoid arthritis (RA) controls and normal controls (NC) combined; NA = not applicable; ESR = erythrocyte sedimentation rate; ND = not determined.

substantially higher than that in the PFS patients. Likewise, the mean HVA concentrations in the RA patients and the healthy controls were similar and were much higher than that measured in patients with PFS. This was not the case for the 5-HIAA concentrations. The mean concentration of 5-HIAA in the RA subgroup was more than 2-fold higher than the mean in the PFS patients, but the mean from the healthy subjects was only 18% higher than that in the PFS group.

Scatter plots of the individual values found for each subject are shown in Figure 1. It is evident that the PFS patient values for each metabolite were clustered narrowly toward the low end of each scale, while values for the non-PFS controls were spread widely through the range of measured concentrations. The contributions of the RA patients and the healthy subjects to the values found for the non-PFS control group overall can be clearly discerned from the individual subject data shown in Figure 1.

As shown in Table 3, there was only 1 significant correlational relationship between any of the 3 biogenic amine metabolites measured in the CSF of PFS patients in this study. PFS patient 5-HIAA concentrations correlated significantly with HVA concentrations ($r = 0.49$, $P = 0.046$; $n = 17$). That relationship was not unique to the PFS patient CSF: As illustrated in Figure 2, similar results were found in the non-PFS samples, strengthening the overall correlation ($r = 0.69$, $P < 0.0001$; $n = 29$).

Of the other neurotransmitters previously measured in the same PFS CSF samples (21–23), only 1 showed a correlation with a biogenic amine measured in the present study (Table 3). HVA levels correlated significantly with the previously measured dynorphin-A concentrations ($r = 0.55$, $P = 0.026$; $n = 16$). None of the CSF biogenic amine levels correlated with levels of substance P, which were elevated (21).

There was no correlation between age and 5-HIAA levels among the PFS patients ($P = 0.74$). In contrast, a significant relationship between age and 5-HIAA levels was apparent both for all subjects combined (PFS + non-PFS subjects $r = 0.5$, $P < 0.006$) and for the non-PFS controls as a group ($r = 0.7$, $P = 0.007$).

Table 2. Biogenic amines in the cerebrospinal fluid of the patients with primary fibromyalgia/fibrositis syndrome (PFS) and control subjects*

Study group (n)	Age (years)	MHPG (ng/ml)	5-HIAA (ng/ml)	HVA (ng/ml)
PFS patients (17)	45.9 ± 2.1	5.76 ± 0.72†	18.19 ± 1.46‡	26.09 ± 1.90§
Non-PFS controls (12)	44.8 ± 4.6	7.77 ± 0.77	29.39 ± 4.97	41.89 ± 4.39
RA (5)	60.8 ± 3.0	7.53 ± 1.59	40.50 ± 9.20	42.28 ± 8.04
NC (7)	32.6 ± 1.8	7.94 ± 1.02	21.45 ± 3.49	41.61 ± 5.48

* Values are the mean ± SEM. MHPG = 3-methoxy-4-hydroxyphenethylene glycol; 5-HIAA = 5-hydroxyindole acetic acid; HVA = homovanillic acid; Non-PFS = rheumatoid arthritis (RA) controls and normal controls (NC) combined.
† $P = 0.028$ versus non-PFS controls.
‡ $P = 0.057$ versus non-PFS controls.
§ $P = 0.005$ versus non-PFS controls.

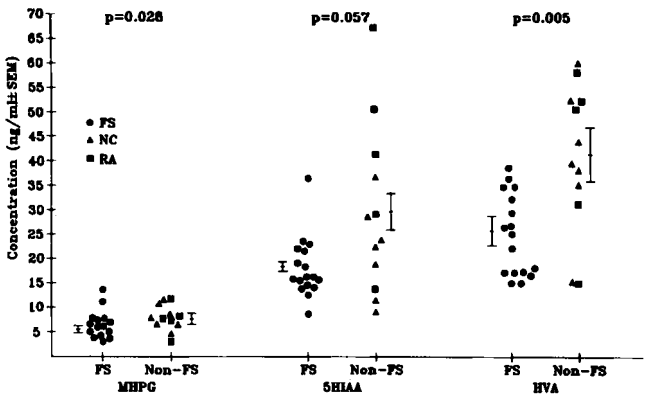

Figure 1. Scatter plots of the concentrations of the biogenic amine metabolites 3-methoxy-4-hydroxyphenethylene glycol (MHPG), 5-hydroxyindole acetic acid (5HIAA), and homovanillic acid (HVA) in the cerebrospinal fluid of patients with fibromyalgia/fibrositis syndrome (FS) and in control subjects (Non-FS). The Non-FS group was composed of patients with rheumatoid arthritis (RA) and normal controls without musculoskeletal pain (NC). Bars show the mean ± SEM. *P* values compare the FS group with the Non-FS group.

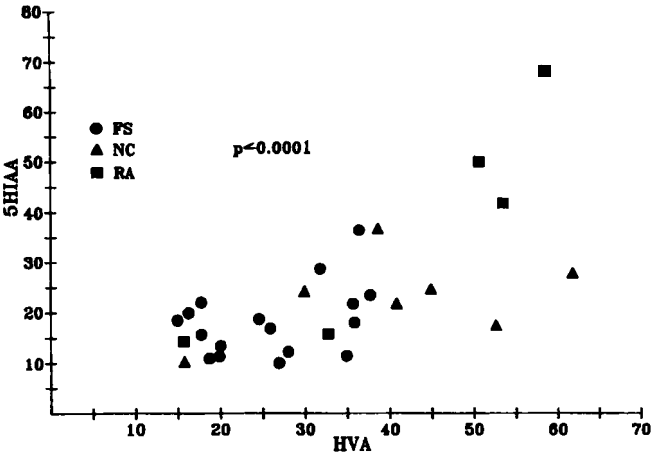

Figure 2. Scatter plot of the correlation between 5-hydroxyindole acetic acid (5HIAA) levels and homovanillic acid (HVA) levels in the cerebrospinal fluid of patients with fibromyalgia/fibrositis syndrome (FS), patients with rheumatoid arthritis (RA), and normal controls (NC). For the group of all 29 subjects, Pearson's 2-tailed correlation (r) was 0.69 ($P < 0.0001$). A significant correlation was also found in the FS group alone (r = 0.49, $P = 0.046$; n = 17).

DISCUSSION

Patient enrollment and acquisition of CSF for this study were completed before the new diagnostic criteria for fibromyalgia were published (28). However, all of the PFS patients did meet the requirements of 2 sets of criteria published earlier (1,24). It is likely, therefore, that the PFS patients in this study are representative of patients with the disorder as it is currently defined. By extrapolation, we propose that the observed abnormalities in CSF biogenic amine metabolites are also representative.

Table 3. Correlations between cerebrospinal fluid (CSF) levels of biogenic amines and CSF levels of other neurotransmitters in patients with primary fibromyalgia/fibrositis syndrome*

	5-HIAA	HVA	SP	MA6P7	Dyn-A	β-End	CGRP
MHPG	0.18	0.10	0.31	0.07	−0.15	−0.26	−0.45
5-HIAA		0.49†	−0.10	−0.05	0.20	−0.33	−0.02
HVA			−0.15	0.31	0.55‡	−0.01	−0.22
SP				0.17	−0.04	0.18	0.36
MA6P7					0.40	0.50	−0.26
Dyn-A						0.20	0.30
β-End							0.01

* Correlational analysis was performed by Pearson's 2-tailed test using the mean of 2 measurements. Except where otherwise indicated, all correlations were nonsignificant ($P \geq 0.05$). 5-HIAA = 5-hydroxyindole acetic acid; HVA = homovanillic acid; SP = substance P; MA6P7 = metenkephalin-arg-6-phe-7; Dyn-A = dynorphin-A; β-End = β-endorphin; CGRP = calcitonin gene-related peptide; MHPG = 3-methoxy-4-hydroxyphenethylene glycol.
† $P = 0.046$ (n = 17).
‡ $P = 0.026$ (n = 16).

Examination of serotonin biochemistry in the CNS of patients with PFS was a logical extension of previous studies in which abnormal levels were found in the blood (18–20). Additional support for the notion that PFS involves a functional deficiency of serotonin comes from the findings of elevated levels of serotonin reuptake receptors on peripheral platelets (19) and lower-than-normal natural killer cell activity in these patients (29,30). The theory that the pathogenesis of PFS is related to a serotonin deficiency is further strengthened by findings regarding which drugs are effective in the treatment of PFS (31,32). PFS is a common cause of musculoskeletal symptoms in patients with the acquired immunodeficiency syndrome (AIDS) (33). Thus, it is of interest that levels of serum tryptophan, CSF tryptophan, serum serotonin, and platelet serotonin are all low in AIDS patients (34).

We measured the metabolite 5-HIAA, rather than serotonin, in the CSF because the normal CSF concentration of serotonin is so low that available measurement tools do not have adequate thresholds of sensitivity (35). Low levels of 5-HIAA in the CSF probably result from subdued metabolism of serotonin. The clinical manifestations of PFS may then occur because serotonin is less readily available for neuroregulation of pain perception and deep sleep. Simultaneous abnormalities in the levels of other biogenic amine metabolites suggest that the serotonin deficit may be just one facet of a more global process.

The observed relationship between 5-HIAA and HVA concentrations in the CSF has been recognized previously (36) but is not well understood. The close correlation between HVA levels and levels of the polypeptide dynorphin A also seems enigmatic. The lack of correlation between elevated levels of substance P and abnormalities in biogenic amine levels in the same CSF samples highlights the complexity of PFS and mandates that studies parallel to those from which these data are derived be undertaken to determine whether the results can be replicated.

It would appear from the medical literature (37–39) that there is no relationship between age and CSF levels of 5-HIAA. No such correlation was found among adolescents ages 6–17 years with recognized behavior disorders (37). In another study (38), 13 healthy individuals whose ages ranged between 20 and 40 years were found to have gradually decreasing 5-HIAA levels with age, but the only subject over 50 years of age exhibited a substantially higher value. No relationship of CSF 5-HIAA to age was found among 30 male inpatients with depression, ranging in age from 16 to 66 (39). The relatively strong relationship between age and 5-HIAA levels found among all subjects combined and among the non-PFS controls in the present study may, therefore, be diagnosis dependent. More data are needed on CSF 5-HIAA levels in healthy individuals between the ages of 50 and 80, to clarify this.

Although this is the first full published report on CSF biogenic amines in PFS (and in RA), an abstract presented by Houvenagel et al in 1990 (40), simultaneously with the presentation of the present work in abstract form, indicated similar findings. Those authors observed significantly lower concentrations of 5-HIAA in the CSF of PFS patients when compared with pain-free normal controls and patients with back pain.

When interpreting the current data, one should take into account several deficiencies inherent in the study design. The control groups were not case-matched for numbers of subjects, age, sex, duration of disease, severity of symptoms, or date of lumbar puncture. Obtaining CSF from matched controls is more difficult than sampling blood or urine. Seasonal variation (41) must also be considered in prospective studies designed to evaluate biogenic amine metabolite concentrations in the CSF, but time of day (42) and diet (43) are apparently irrelevant.

The number of subjects in the present study was small. However, any anticipated error related to low numbers of subjects should be Type I rather than Type II, so the differences observed may be valid. Since all of our subjects were of Scandinavian descent, the results may not be representative of PFS patients, RA patients, or even normal controls of other genetic backgrounds. The similar findings in the parallel study by Houvenagel et al (40), however, mitigate against the latter two concerns.

The CSF used in this study was obtained from a lumbar site rather than from the ventricles of the brain, which are connected more intimately with brain metabolism. It is recognized that the absolute concentrations of CSF constituents do change during passage from the cisterna to the lumbar area (44). While the HVA concentration may drop by as much as 6-fold, that of 5-HIAA falls by only about 3-fold in transit down the spinal canal. Despite those changes, the lumbar-level spinal fluid concentrations of both metabolites should remain proportional to cisternal concentrations. A previous investigation (45) revealed a high correlation between plasma and CSF 5-HIAA concentrations, so the low levels of 5-HIAA observed in our PFS patients are consistent with low serum levels of serotonin found in other patients with PFS (18).

The CSF samples analyzed in this study were stored at −70°C for approximately 2 years before their biogenic amine metabolite concentrations were analyzed. There is a precedent for misinterpretation of CSF component measurements following storage at −45°C (46). Available evidence (27,47) would suggest, however, that the biogenic amine metabolites remain stable when kept in the dark at −70°C. Furthermore, the CSF samples from the non-PFS controls were stored under identical conditions to those used for the PFS CSF, and showed values that were in the normal range.

We did not consider it appropriate to discontinue immunosuppressive medications taken by the RA patients prior to their lumbar puncture. There are no data from which to predict what influence such drugs might have on biogenic amine levels.

The severity of symptoms in the individual PFS patients was not documented sufficiently to allow an investigation of correlations between disease severity and biogenic amine metabolite concentrations. A new, prospective study, whose design will enable exploration of this question, is currently under way.

The results of this pilot investigation give rise to several interesting speculations. It may be that the metabolite concentrations in the fibromyalgia patients are low, and the intersubject variability small, because these metabolites are all subject to global inhibition

from a higher neurologic level. Since abnormalities have now been found in both the serum and the CSF, the underlying defects probably involve both the central and peripheral nervous systems. These abnormalities are more likely to be responsible for the symptoms experienced by PFS patients, than to be the consequences of chronic pain, as supported by findings of more normal levels among RA patients in the present investigation and among patients with chronic low back pain (40). A better understanding of these phenomena must await confirmation in larger numbers of PFS patients, in studies comparing them with case-matched controls.

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REFERENCES

1. Yunus M, Masi AT, Calabro JJ, Miller KA, Feigenbaum SL: Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. Semin Arthritis Rheum 11:151–171, 1981
2. Wolfe F, Hawley DJ, Cathey MA, Caro XJ, Russell IJ: Fibrositis: symptom frequency and criteria for diagnosis: an evaluation of 291 rheumatic disease patients and 58 normal individuals. J Rheumatol 12:1159–1163, 1985
3. Campbell SM, Clark S, Tindall EA, Forehand ME, Bennett RM: Clinical characteristics of fibrositis. I. A "blinded," controlled study of symptoms and tender points. Arthritis Rheum 26:817–824, 1983
4. Alarcón-Segovia D, Ramos-Niembro F, González-Amaro RF: One thousand private rheumatology patients in Mexico City (letter). Arthritis Rheum 26:688–689, 1983
5. Russell IJ, Fletcher EM, Tsui J, Michalek JE: Comparisons of rheumatoid arthritis and fibrositis/fibromyalgia syndrome using functional and psychological outcome measures (abstract). Arthritis Rheum 32 (suppl 4):S70, 1989
6. Cathey MA, Wolfe F, Kleinheksel SM: Functional ability and work status in patients with fibromyalgia. Arthritis Care Res 1:85, 1988
7. Hamm C, Derman S, Russell IJ: Sleep parameters in fibrositis/fibromyalgia syndrome (abstract). Arthritis Rheum 32 (suppl 4):S70, 1989
8. Moldofsky H, Scarisbrick P, England RE, Smythe H: Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. Psychosom Med 37:341–351, 1975
9. Yunus MB, Kalyan-Raman UP, Masi AT, Aldag JC: Electron microscopic studies of muscle biopsy in primary fibromyalgia syndrome: a controlled and blinded study. J Rheumatol 16:97–101, 1989
10. Bartels EM, Danneskiold-Samsoe B: Histological abnormalities in muscle from patients with certain types of fibrositis. Lancet I:755–757, 1986
11. Henriksson KG, Bengtsson A, Larsson J, Lindstrom F, Thornell LE: Muscle biopsy findings of possible diagnostic importance in primary fibromyalgia (fibrositis, myofascial syndrome). Neurologia 38:213–221, 1989
12. Bengtsson A, Henriksson KG, Larsson J: Reduced high-energy phosphate levels in the painful muscles of patients with primary fibromyalgia. Arthritis Rheum 29:817–821, 1986
13. Kellgren JH: Observations on referred pain arising from muscle. Clin Sci 3:175–190, 1938
14. Cohen ML, Arroyo JF, Champion GD: Evidence for neuropathic mechanisms in diffuse musculoskeletal pain syndrome (fibromyalgia) (abstract). Arthritis Rheum 33 (suppl 9):S22, 1990
15. Moldofsky H, Warsh JJ: Plasma tryptophan and musculoskeletal pain in non-articular rheumatism ("fibrositis syndrome"). Pain 5:65–71, 1978
16. Harvey JA, Schlosberg AJ, Yunger LM: Behavioral correlates of serotonin depletion. Fed Proc 34:1796–1801, 1975
17. Murphy RM, Zemlan FP: Differential effects of substance P on serotonin-modulated spinal nociceptive reflexes. Psychopharmacology (Berl) 93:118–121, 1987
18. Russell IJ, Michalek JE, Vipraio GA, Fletcher EM, Javors MA, Bowden CL: Serum serotonin and platelet ^{3}H-imipramine binding receptor density in patients with fibromyalgia/fibrositis syndrome. J Rheumatol 19:104–109, 1992
19. Russell IJ, Michalek JE, Vipraio GA, Fletcher EM, Wall K: Serum amino acids in fibrositis/fibromyalgia syndrome. J Rheumatol 16:158–163, 1989
20. Yunus MB, Dailey JW, Masi AT, Aldag JC, Jobe PC: Abnormal transport ratio of serum tryptophan in primary fibromyalgia (abstract). Arthritis Rheum 33 (suppl 9):S55, 1990
21. Vaeroy H, Helle R, Førre Ø, Kåss E, Terenius L: Elevated CSF levels of substance P and high incidence of Raynaud's phenomenon in patients with fibromyalgia: new features for diagnosis. Pain 32:21–26, 1988
22. Vaeroy H, Helle R, Førre Ø, Kåss E, Terenius L: Cerebrospinal fluid levels of β-endorphin in patients with fibromyalgia (fibrositis syndrome). J Rheumatol 15:1804–1806, 1988
23. Vaeroy H, Nyberg F, Terenius L: No evidence for endorphin deficiency in fibromyalgia from measurement

of CSF dynorphin A and met-enkephalin-arg6-phe7. Pain (in press)
24. Smythe HA, Moldofsky H: Two contributions to understanding of the "fibrositis" syndrome. Bull Rheum Dis 28:928, 1977
25. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, Medsger TA Jr, Mitchell DM, Neustadt DH, Pinals RS, Schaller JG, Sharp JT, Wilder RL, Hunder GG: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31:315–324, 1988
26. Wolfe F, Cathey MA, Kleinheksel SM, Amos SP, Hoffman RG, Young DY, Hawley DJ: Psychological status in primary fibrositis and fibrositis associated with rheumatoid arthritis. J Rheumatol 11:500–506, 1984
27. Javors MA, Bowden CL, Maas JW: MHPG, 5HIAA, and HVA in human CSF: storage and measurement by reversed phase high performance liquid chromatography (HPLC) and coulometric detection using MHPLA as an internal standard. J Chromatogr 336:259–269, 1984
28. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP: The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. Arthritis Rheum 33:160–172, 1990
29. Russell IJ, Vipraio GA, Tovar Z, Michalek J, Fletcher E: Abnormal natural killer cell activity in fibrositis syndrome is responsive in vitro to IL-2 (abstract). Arthritis Rheum 31 (suppl 4):S24, 1988
30. Hellstrand K, Hermodsson S: Role of serotonin in the regulation of human natural killer cell cytotoxicity. J Immunol 139:869–875, 1987
31. Goldenberg DL, Felson DT, Dinerman H: A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. Arthritis Rheum 29:1371–1377, 1986
32. Gatter RA: Pharmacotherapeutics in fibrositis. Am J Med 81 (suppl 3A):63–66, 1986
33. Buskila D, Gladman DD, Langevitz P, Urowitz S, Smythe HA: Fibromyalgia in HIV infection. J Rheumatol 17:1202–1206, 1990
34. Larsson M, Hagberg L, Norkrans G, Forsman A: Indole amine deficiency in blood and cerebrospinal fluid from patients with human immunodeficiency virus infection. J Neurosci Res 23:441–446, 1989
35. Anderson GM, Mefford IN, Tolliver TJ, Riddle MA, Ocame DM, Leckman JF, Cohen DJ: Serotonin in human lumbar cerebrospinal fluid: a reassessment. Life Sci 46:247–255, 1990
36. Davis JM, Koslow SH, Gibbons RD, Maas JW, Bowden CL, Casper R, Hanbin I, Javaid JI, Chang SS, Stokes PE: Cerebrospinal fluid and urinary biogenic amines in depressed patients and healthy controls. Arch Gen Psychiatry 45:705–717, 1988
37. Kruesi MJP, Swedo SE, Hamburger SD, Potter WZ, Rapoport JL: Concentration gradient of CSF monoamine metabolites in children and adolescents. Biol Psychiatry 24:507–514, 1988
38. Larsson M, Forsman A, Hallgren J: HPLC assays of 5-HIAA and tryptophan in blood: a methodological study with clinical applications. Methods Find Exp Clin Pharmacol 10:453–460, 1988
39. Faustman WO, Faull KF, Whiteford HA, Borchert C, Csernansky JG: CSF 5-HIAA, serum cortisol and age differentially predict vegetative and cognitive symptoms in depression. Biol Psychiatry 27:311–318, 1990
40. Houvenagel E, Forzy G, Cortet B, Vincent G: 5-hydroxy indol acetic acid in cerebrospinal fluid in fibromyalgia (abstract). Arthritis Rheum 33 (suppl 9):S55, 1990
41. Swedo SE, Kruesi MJP, Leonard HL, Hamburger SD, Cheslow DL, Stepetic M, Potter WZ: Lack of seasonal variation in pediatric lumbar cerebrospinal fluid neurotransmitter metabolite concentrations. Acta Psychiatr Scand 80:644–649, 1989
42. Menachem EB, Persson L, Schechter PJ, Haegele KD, Huebert N, Hardenberg J: Cerebrospinal fluid parameters in healthy volunteers during serial lumbar punctures. J Neurochem 52:632–635, 1989
43. Teff KL, Young SN, Marchand L, Botez MI: Acute effect of protein or carbohydrate breakfasts on human cerebrospinal fluid monoamine precursor and metabolite levels. J Neurochem 52:235–241, 1989
44. Degrell I, Nagy E: Concentration gradients for HVA, 5-HIAA, ascorbic acid, and uric acid in cerebrospinal fluid. Biol Psychiatry 27:891–896, 1990
45. Sarrias MJ, Cabre P, Martinez E, Artigas F: Relationship between serotoninergic measures in blood and cerebrospinal fluid simultaneously obtained in humans. J Neurochem 54:783–786, 1990
46. Hadler NM, Gerwin RD, Frank MM, Whitaker JN, Baker M, Decker JL: The fourth component of complement in the cerebrospinal fluid in systemic lupus erythematosus. Arthritis Rheum 16:507–521, 1973
47. Hattox SE: Methods for determining MHPG in plasma, CSF, and urine, MHPG: Basic Mechanisms and Psychopathology. Edited by JW Maas. New York, Academic Press, 1983