Regional cerebral blood flow and cytokines in young females with fibromyalgia

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Abstract

Objective

To determine whether there is any difference in regional cerebral blood flow (rCBF) and serum cytokine levels and association between clinical parameters and rCBF and serum cytokine levels in young females with fibromyalgia (FM). The other aim was to search whether the depression state has any effect on these two parameters.

Methods

Nineteen women with FM and 20 healthy women had ^{99m}Tc-HMPAO brain single-photon-emission computed tomography (SPECT) to evaluate rCBF. Serum interleukin (IL) levels (IL 1β, IL 2r, IL 6 and IL 8) were measured. Clinical and psychological evaluation was also carried out in FM patients and healthy controls.

Results

The patients with FM had significantly higher radioactivity uptake ratio in right and left caudate nucleus ($p = 0.009$, $p = 0.001$, respectively) than healthy controls. There was statistically significant decrease in the ^{99m}Tc-HMPAO uptake in the right superior parietal ($p = 0.041$), gyrus rectalis ($p = 0.036$) and pons ($p = 0.023$). FM patients had significantly higher serum IL 2r and IL 8 levels ($p = 0.023$, $p = 0.011$, respectively) than controls. Additionally, FM patients had significantly higher Fibromyalgia Impact Questionnaire (FIQ), Health Assessment Questionnaire (HAQ), and Hamilton Depression Rate scale (HDRS) scores ($p = 0.000$) than controls. Interestingly, the patients with mild depressive symptoms or without (i.e.HDRS-score ≤ 16) had significantly higher serum IL 8 levels ($p = 0.027$) and increased radioactivity uptake ratio in the pons ($P = 0.036$) than the patients with more severe depressive symptoms (i.e. HDRS-score > 16). With regard to regional cerebral blood flow, significant correlations were detected between RSP and morning stiffness ($r = 0.70$, $p < 0.01$) and sleep disturbance ($r = -0.53$, $p < 0.05$), and between gyrus rectalis and FIQ score. There were significant correlations between LCN and IL-2 ($P = 0.025$), between RSP and morning stiffness ($P = 0.006$), sleep disturbance ($P = 0.021$) according to multiple regression analysis test.

Conclusion

This study shows a significant increase in rCBF of caudate nuclei, a reduction in the pons, some cortical regions activity and a increase in IL 8, IL2r levels of young female patients with FM. These findings are more prominent in patients with low HDRS scores.

Key words

Depression, cytokines, fibromyalgia, regional cerebral blood flow.

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Introduction

Fibromyalgia is a disorder characterised by pain in the muscles and soft tissues, severe fatigue and often associated with anxiety and depression (1). To date many hypothesis about its aetiology have been suggested, however none of them has been proved yet. One of the favoured hypotheses is immunologic component of the FM and the role of cytokines. The other one is the effect of regional cerebral blood flow (rCBF) disturbances on pain perception of the patients with FM. Another is about its psychomatic or psychiatric origin related to major depression (2,3). In this study we aimed to evaluate these two hypotheses. We researched cytokine levels and rCBF distribution in patients with FM.

Proinflammatory cytokines, such as IL 1 and IL 6, may induce hyperalgesia, for example, by acting on the forebrain tissue surrounding lateral and third ventricle. Thus they may directly influence the responsiveness of nociceptive neurones (4-7). In experimental animal or human studies, IL 1 and IL 6 may not only induce (inflammatory) hyperalgesia but also other symptoms characteristic of fibromyalgia, such as fatigue, sleep disorders and depression-like symptoms (8, 9). We anticipated that the signs of an activated inflammatory response system (IRS) and significant positive correlations between IRS markers and severity of the disease might be found in fibromyalgia because of the following: (i) fibromyalgia may be an inflammatory disorder; (ii) proinflammatory cytokines may induce the characteristic symptoms of fibromyalgia. More specifically, since increased serum concentrations of interleukin-6 (IL 6), soluble IL 6 receptor (s IL 6r), and sIL 1r antagonist (sIL 1rA) have been found in patients with inflammatory disorders and major depression (10), we expected to find the same alterations in fibromyalgia patients (11).

Regional cerebral blood flow (rCBF) is known to be a very sensitive indicator of cerebral dysfunction. Evaluation of rCBF is available with single photon emission computed tomography (SPECT). High-resolution images can now be achieved by SPECT because of the significant advancement in SPECT technology and the commercial availability of regional cerebral perfusion tracers labelled with technetium-99m (^{99m}Tc-HMPAO) (12).

Several researchers have evaluated rCBF of patients with FM. However, different and controversial results have been achieved (13,14). Mountz *et al.* (13), showed that people with fibromyalgia had diminished cerebral blood flow meaning less functional activity in the thalamus and the right- left caudate nucleus. Kwiatek *et al.* (14) showed significant decrease in cerebral blood flow in the right hemi thalamus and inferior pontin tegmentum, but not left hemi thalamus, and right and left caudate nuclei of patients with FM compared with the control group.

Our aim is to determine if there is any difference in serum cytokine levels and rCBF values between patients with FM and healthy control subjects, and is to search whether there is any association between depressive symptoms and these two parameters.

Patients and methods

Patients and control subjects

Twenty healthy volunteers and 19 patients with FM who were diagnosed by the Department of Physical Therapy and Rehabilitation (University Hospital of Dicle, Diyarbakir, Turkey) participated in the study. All subjects were young than 35 years. Patients fulfilled the American College of Rheumatology (ACR) criteria for fibromyalgia (15). These criteria include: (a) a history of widespread pain for at least 3 months, i.e. pain in the left side of the body, pain in the right side of the body, pain above and below the waist, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back pain); and (b) presence of at least 11 tender point sites (measurements performed using digital palpation with a force of 4 kg.): occiput L(left) or R (right), low cervical L or R, trapezius L or R, supraspinatus L or R, second rib L or R, lateral epicondyle L or R, gluteal L or R, and knee L or R.

Major clinical conditions other than fibromyalgia were excluded by physical

examination and routine whole blood cells counting, hematocrit, hemoglobulin, baseline thyroid-stimulating hormone and antinuclear auto antibodies studies. Common exclusionary criteria for fibromyalgia patients and normal controls were: (a) a recent or past history of psychiatric disorders, e.g. major depressive disorder, alcohol addiction, substance abuse, schizophrenic or paranoid disorder, personality disorders, and somatoform disorders (patients who had received fluoxetine within 6 weeks, MAO inhibitors within 2 weeks, other psycho-active drugs within 1 week and anti-inflammatory drugs within 4 weeks before baseline); (b) immunocompromised subjects; (c) subjects with neurological, inflammatory, endocrine or clinically significant chronic disease, such as diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, and organic brain disorders; (c) abnormal liver function tests, such as serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphates, and gamma-glutamyl transpeptidase; and (d) pregnant females. All patients denied earlier infections of the CNS and none reported head trauma with unconsciousness. A neurologist had excluded specific neural disease.

Orthopaedic diseases that may be a cause of the pain, had excluded by the examination of an orthopaedic surgeon. Rheumatic or other inflammatory diseases had been excluded by laboratory test procedures and clinical examination. All subjects were free of any infections, inflammatory or allergic reactions for at least 2 weeks prior to the blood sampling and free of drugs known to affect immune or endocrine functions and of hormonal preparations. Each patient had normal findings on radiographs of the chest, hands, feet, and sacroiliac joints. Each patient had been examined by a rheumatologist to ensure that they met the ACR criteria for FM and to rule out the presence of any other rheumatic disorder, including chronic fatigue syndrome. Thus, the patients' symptoms could be attributed solely to FM.

The control group consisted of 20 healthy, educations level and age-matched volunteers. The subjects were mainly selected by local advertisement. All participants gave informed consent prior to entry.

Clinical and psychological evaluation

Eighteen ACR FM tender points and 18 control points were examined on both occasions in symmetric pairs in computer-generated random order. The pairs of control points were 5 cm superior to the orbit, middeltoid, distal third of the dorsal forearm, thumbnail, costal margin in the midaxillary line, inner lower quadrant of the buttock, 5 cm inferior to the anterior superior iliac spine, anteromedial surface of the midtibia, and midpoint of the dorsum of the third metatarsal bone. In response to an estimated digital force of 4 kg, subjects were asked to indicate whether they felt any discomfort (score 0), tenderness (score 1), or pain (score < 2). Pain with no grimace, flinching, or withdrawal was scored as 2; pain with flinching or withdrawal was scored as 3; and pain with marked flinching or withdrawal was scored as 4.

All patients were evaluated by physician about the intensity of pain, skinfold tenderness, fatigue, muscle spasm, sleep disturbances, morning stiffness. Evaluations were carried out according to Likert scale (16). At the end of the tender point examination, each subject was given a copy of the Fibromyalgia Impact Questionnaire (FIQ) (17), Health Assessment Questionnaire (HAQ) (18), and Hamilton Depression Rate Scale (HDRS) (19). All papers were completed and returned prior to SPECT imaging.

For each subject, the respective totals of initial and subsequent manual tender point examination scores at all ACR tender point sites were averaged to provide an overall mean tender point index (TPI; range 0-72) (27). A mean control point index (CPI) was similarly calculated. Also, a mean tender point count (TPC; range 0-18) was computed from the initial and subsequent scores for each ACR tender point site (a tender point was considered positive with a score of < 2) (15).

We divided the fibromyalgia patients into two groups: 1) HDRS >16, indicating substantial depressive symptoms, (9 patients) and 2) HDRS ≤ 16 (10 patients) in order to assess the effect of depressive symptoms on the serum cytokines and rCBF.

Measurements of serum cytokines

After the baseline screening, which consisted of physical examination, checking the inclusion and exclusion criteria and blood samplings for blood routine screening, patients underwent a 1-week drug-free period. Hereafter, blood was sampled for the assay of IL 1, IL 2r, IL 6 and IL 8 after an overnight fasting. Blood collection was performed in standardised conditions in order to minimise sources of preanalytical variation. Serum IL 1β, IL 6, IL 8 and sIL 2r levels were determined with IMMULITE diagnostic kits (DPC-Diagnostic Products Corporation, USA). We measured IL 1β (normal range 0-5 pg/ml), IL 6 (normal range 0-5.4 pg/ml), IL 8 (normal range 0-62 pg/ml) and sIL 2r (normal range 223-710 U/ml). The assays have undergone extensive testing with a multitude of different cytokines to ensure absence of cross-reactivity with other molecules.

Brain SPECT scanning

As we have not MRI and SPECT co-registration system we have used a normal brain morpho-functional atlas as a reference material to choose appropriate slices and regions we have interested in (20).

In this study rCBF brain SPECT images were obtained by the GE Millennium single-head rotating gamma camera system, equipped with low energy general-purpose parallel hole collimator. Although it is known that a high-resolution collimatore is used for brain SPECT studies we were not able to use it as the nuclear medicine department has not this equipment. As a brain perfusion tracer 99-m technetium-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) was used. 20mCi ^{99m}Tc-HMPAO were injected intravenously using a small butterfly intravenous catheter, while patient was at rest with eyes closed in a quite dimly lit room in the Nuclear Medicine Department. Ten minutes after injection the subject was

placed in a supine position on the scan bad. Scan bad and head of the camera were arranged to achieve the minimum radius of rotation of the detector. As a single head rotating Anger gamma camera system used the head rotated 360° at 2.8° increaments at 20 seconds per stop to acquire an image. Data were projected into a 128 x 128 matrix size. After the completion of the scan, data were stored and analysed in a workstation computer (GE Laboratories). Images reconstruction was performed by filtered back projection of the 128 acquired projections, using a Butterworth filter with a frequency cut-off 0.5 cycles/cm order 10. After attenuation correction, images were oblique reconstructed parallel to orbithomeatal line.

Transverse scan sections were used for the brain SPECT images analysis by semiquantitative technique. Region of interests (ROI) were 19 different cortical regions, right-left caudate nuclei (RCN-LCN), right-left hemithalamus (RH-LH), pons and cerebellum. Cortical regions were right superior frontal (RSF), right middle frontal (RMF), right inferior frontal (RIF), left superior frontal (LSF), left middle frontal (LMF), left inferior frontal (LIF), right superior temporal (RST), right middle temporal (RMT), right inferior temporal (RIT), left superior temporal (LST), left middle temporal (LMT), left inferior temporal (LIT), right superior parietal (RSP), right inferior parietal (RIP), left superior parietal (LSP), left inferior parietal (LIP), right occipital (ROX), left occipital cortex (LOX) and gyrus rectalis (GR). Average counts for each ROI were obtained. They were normalised by dividing these values by average count of the cerebellum (Fig. 1).

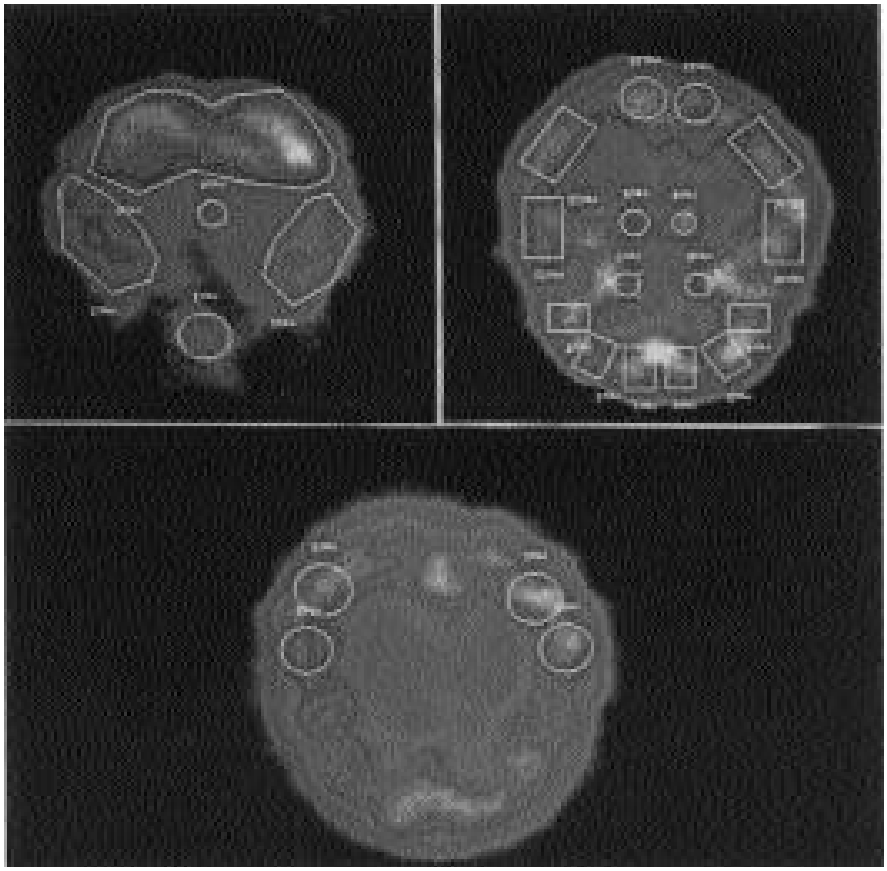

Fig. 1. Three transverse sections used to semiquantify regional cerebral uptake values of regional cerebral blood flow (rCBF). Semiquantitative data are obtained by normalising the counts in each region of interest (ROI) (over 19 cortical areas,caudate nuclei both hemithalamus and pons) by dividing them by the cerebellar counts. The first part of the picture (above) demonstrates roi 0, roi 1, roi 2, roi 3, meaning regions of interest over the right superior parietal, right inferior parietal, left superior parietal and left inferior parietal cortical regions, respectively. Second part of the picture (left below) demonstrates roi 0, roi 1, roi 2, roi 3, roi 4, roi 5, roi 6, roi 7, roi 8, roi 9, roi 10, roi 11, roi 12, roi 13, roi14, roi 15, meaning right superior frontal, left superior frontal, right middle frontal,left middle frontal, right inferior frontal, left inferior frontal cortex, right caudate nucleus,left caudate nucleus, right thalamus, left thalamus, right superior temporal,left superior temporal, right inferior temporal,left inferior temporal, right occipital and left occipital cortex, respectively. In the third part of the picture (right below), roi 0, roi 1, roi 2, roi 3, roi 4 represent regions of interest over the cerebellum, right inferior temporal, left inferior temporal cortex and gyrus rectalis, respectively.

Statistical analysis

Statistical analyses were done by SPSS 8.0 PC program. Results were expressed as means ± SD (standard deviation). Findings in fibromyalgia patients and controls were compared using Mann-Whitney U test. The non-parametric Spearman correlation test was used for correlation analysis. Multiple regression analysis test was used for identify the most important correlations among the various variables. Results were considered to be significant at $p < 0.05$.

Results

Demographic and clinical variables, interleukin levels, quality of life, and psychological distress

As shown in Table I, there was no significant difference in mean age or education level between both groups. Thus, differences between patients and controls in any variables discussed below cannot be attributed to between-group variations in demographic factors. All the patients and controls were female. Duration of disease was 22.10 ± 11.40 months in patients with FM.

With regard to mean TPC, TPI, CPI, and other clinical symptoms Table I shows that patients with FM displayed significantly higher values than controls ($p = 0.000$). With regard to serum interleukin levels, table 1 shows that, patients with FM had significantly higher serum IL 2r and IL 8 levels ($p = 0.023$, $p = 0.011$, respectively) than controls. Additionally, with regard to quality life and psychological distress, Table I shows that the patients with FM had significantly higher FIQ, HAQ, and HDRS scores ($p = 0.000$) than controls.

Table I. Clinical measurements of female patients with fibromyalgia and healthy female controls*.

Variables	FM patients (n=19) Mean ± SD	Control subjects (n=20) Mean ± SD	p
Age (year)	28.31±9.05	29.05±6.57	0.812
Education level (year)	7.31±3.28	7.89±2.76	0.783
Duration of pain (month)	22.10±11.40	-	-
Tender point count	13.57±1.95	2.13±0.95	0.000
Tender point index	37.27±10.74	2.21±3.83	0.000
Control point index	18.81±9.72	0.81±1.25	0.000
Fatigue	3.89±0.88	0.33±0.49	0.000
Morning stiffness	2.49±0.87	0.35±0.53	0.000
Sleep disturbance	2.26±1.36	0.41±0.71	0.000
Pain intensity	2.71±0.68	0.43±0.54	0.000
Muscle spasm	1.84±0.61	0.27±0.11	0.000
Skin fold tenderness	2.15±0.89	0.58±0.61	0.000
Interleukin-1β (pg/ml)	5.01±1.33	5.12±1.47	0.688
Interleukin-2r (U/ml)	550.77±181.71	402.5±48.38	0.023
Interleukin-6 (pg/ml)	5.08±0.92	5.15±0.58	0.781
Interleukin-8 (pg/ml)	11.96±3.95	7.94±2.77	0.011
FIQ score	56.4±9.16	13.17±7.21	0.000
HAQ score	1.11±0.45	0.15±0.20	0.000
HDRS score	22.84±4.72	3.58±3.50	0.000

*FIQ= Fibromyalgia Impact Questionnaire; HAQ= Health Assessment Questionnaire; HDRS= Hamilton Depression Rate Scale.

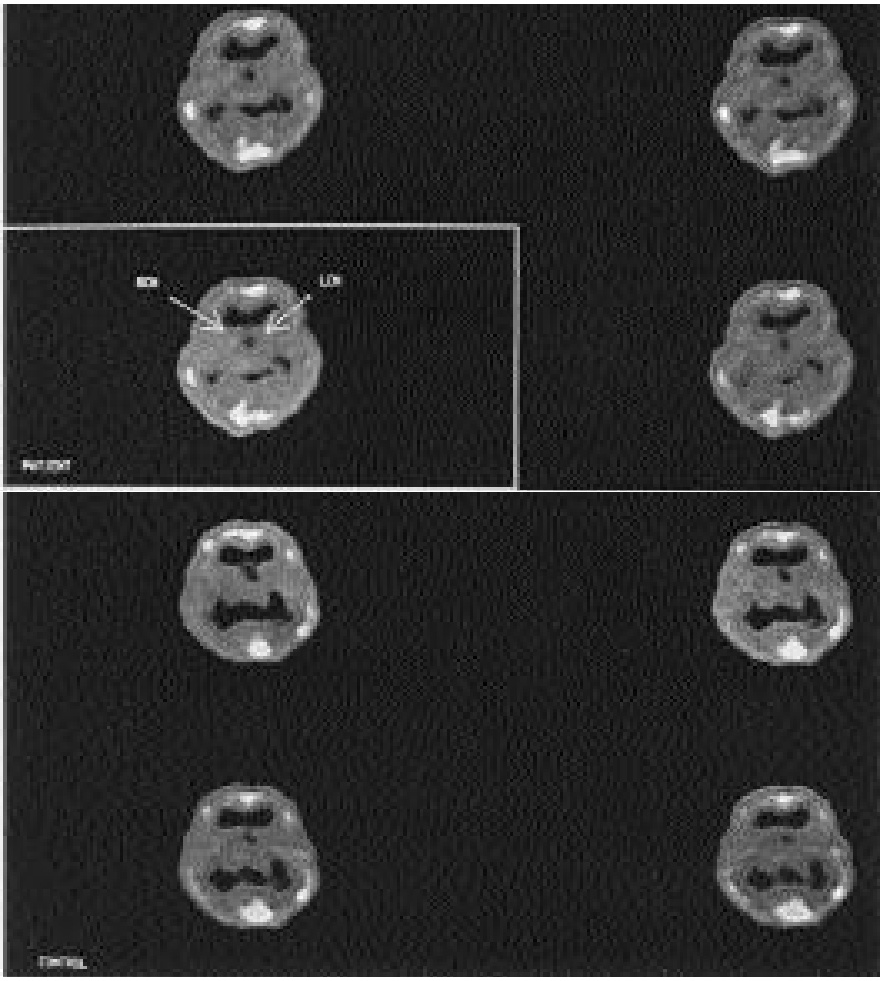

Fig. 2. 99m-technetium-hexamethylpropyleneamine oxime (Tc^{99m}- HMPAO) brain SPECT scan transverse section images from a FM patient and a control subject. There is high blood flow to the right and left caudate nuclei (RCN, LCN) compared to the normal control.

Regional cerebral blood flow

Table II shows that the patients with FM had significantly higher radioactivity uptake ratio in right and left caudate nucleus ($p = 0.009$, $p = 0.001$, respectively) (Fig. 2) than healthy controls. There was a statistically significant decrease in the ^{99m}Tc-HMPAO uptake in the right superior parietal ($p = 0.041$), gyrus rectalis ($p = 0.036$) and pons ($p = 0.023$) (Fig. 3).

With regard to regional cerebral blood flow, significant correlations were detected between RSP and morning stiffness ($r = 0.70$, $p < 0.01$) and sleep disturbance ($r = -0.53$, $p < 0.05$), and between gyrus rectalis and FIQ score ($-r = 0.51$, $p = 0.047$) and between LCN and IL-2 ($r = -0.56$, $p = 0.031$) (Table III). There were significant correlations between LCN and IL-2 ($P = 0.025$), between RSP and morning stiffness ($P = 0.006$), sleep disturbance ($P = 0.021$) according to multiple regression analysis test.

The major finding of this study is that there is a significant difference in the rCBF and cytokines between patients with depressive symptoms and patients who were free of depression. Thus, fibromyalgia patients with more mild depressive symptoms (i.e. HDRS-score <16) have significantly higher serum IL 8 levels ($p = 0.021$) and increased blood flow in the pons ($P < 0.042$) than fibromyalgia patients with more severe depressive symptoms (i.e. HDRS-score > 16).

Discussion and conclusions

No conclusive evidence of an underlying cause or pathophysiologic basis for fibromyalgia exists, although a myriad of mechanisms has been proposed (21). It has been suggested that fibromyalgia has an immunologic component (22-25). Peter and Wallace (24) have been reported an elevation in the level of serum IL 2 in patients with fibromyalgia. Wallace and Margolin (25) reported that cancer patients undergoing intravenous recombinant IL2 therapy experienced fibromyalgia-like symptoms, and they therefore suggested a possible role of IL 2 in the development of fibromyalgia. These two reports suggest that IL 2 may be involved

Table II. Mean ± SD values of regional cerebral blood flow in the right-left caudat nuclei, right-left hemithalamus, pons and 19 different cortical regions of female patients with fibromyalgia and healthy female controls.

Variables	FM patients (n=19) Mean ± SD	Control subjects (n=20) Mean ± SD	P
Right superior frontal	1.022±0.27	1.032±0.31	0.62
Right middle frontal	1.020±0.29	1.018±0.321	0.98
Right inferior frontal	0.978±0.221	1.004±0.431	0.61
Left superior frontal	1.0280.239	1.031±0.324	0.56
Left middle frontal	0.9940.345	1.006±0.238	0.35
Left inferior frontal	0.989±0.342	0.972±0.435	0.51
Right superior temporal	1.022±0.324	1.023±0.298	0.88
Right middle temporal	1.021±0.233	1.039±0.321	0.71
Right inferior temporal	0.756±0.029	0.824±0.236	0.81
Left superior temporal	1.022±0.365	1.025±0.287	0.42
Left middle temporal	1.018±0.128	1.029±0.237	0.74
Left inferior temporal	0.740±0.115	0.783±0.456	0.17
Right superior parietal	0.886±0.243	1.001±0.546	0.04
Right inferior parietal	0.993±0.321	1.004±0.362	0.35
Left superior parietal	0.958±0.254	0.985±0.324	0.81
Left inferior parietal	1.001±0.352	1.020±0.329	0.56
Right occipital	1.045±0.211	1.057±0.328	0.29
Left occipital	1.029±0.104	1.044±0.211	0.15
Gyrus rectalis	0.601±0.217	0.763±0.243	0.03
Right caudat nuclei	0.866±0.235	0.819±0.289	0.009
Left caudat nuclei	0.853±0.121	0.799±0.208	0.001
Right hemithalamus	0.883±0.102	0.874±0.206	0.18
Left hemithalamus	0.882±0.234	0.872±0.126	0.93
Pons	0.709±0.098	0.779±0.117	0.02

Table III. Correlation between regional cerebral blood flow and variables evaluated in patients with fibromyalgia.

Age (year)	0.06	0.06	0.25	0.34	-0.08
Duration of pain (month)	0.21	0.20	-0.20	0.02	-0.12
Tender point count	0.40	0.41	0.25	0.37	-0.08
Morning stiffness	0.70**	-0.07	0.23	0.10	0.27
Fatigue	0.27	-0.20	0.41	-0.05	-0.24
Sleep disturbance	-0.53*	-0.12	-0.08	-0.45	-0.31
Pain intensity	0.20	0.12	0.34	0.05	-0.06
Muscle spasm	0.01	-0.21	0.28	-0.15	-0.12
Skin fold tenderness	0.04	0.36	0.31	-0.23	-0.30
Interleukin-1β	-0.35	-0.09	-0.41	-0.13	0.33
Interleukin-2r	0.39	-0.29	-0.36	-0.56*	-0.21
Interleukin-6	0.24	-0.19	-0.32	-0.13	0.21
Interleukin-8	-0.30	-0.42	-0.40	-0.03	0.21
FIQ score	0.27	-0.51*	-0.39	0.11	0.33
HAQ score	-0.26	-0.41	0.42	0.37	0.15
HDRS score	0.26	0.06	0.21	0.23	-0.23

* $p < 0.05$, *$p < 0.001$

in the symptoms of fibromyalgia.

In addition, Littlejohn *et al*. (26) have reported increased neurogenic inflammation in fibromyalgia. Mast cells produce several cytokines, which can act in both a paracrine and autocrine way when activated. Wallace *et al*. (27) has also been suggested a role for cytokines in FM although the cytokine levels (IL 1, IL 2, IL 2r, TNFα) as measured in serum did not differ between 16 patients and controls. Hader (28) *et al.* found a delayed production of IL2 in patients with FM.

Clinical studies show that more than 75% of patients with fibromyalgia complain of poor sleep (15, 29, 30). IL 1 is believed to be mainly responsible for the coordination of certain immunologic substances and neuroendocrines in the regulation of the sleep-wake cycle. Krueger and Obal (31) have proposed that the diurnal sleep-wake rhythm is the result of oscillatory mechanisms that involve brain IL 1 and the neurohormones of the hypothalamic pituitary axis.

To date, IL 1, IL 2, and IL 6 have been evaluated in various studies. However, we were specifically interested in IL8 in addition to these interleukin types. Surprisingly, we found that IL8 is higher in FM patients than the control cases and the IL8 level is also significantly high in patients whose depression state is low.

Brain SPECT may be a cornerstone to solve the question about the aetiology of FM. However, there are only two rCBF studies in patients with FM and their results are controversial.

To date, seemingly the most direct evidence of alteration in central pain pathway function in FM has been reported in a preliminary cross-sectional study by Mountz *et al.* (13) and Kwiatek *et al.* (14) using the semi quantitative functional brain mapping technique of SPECT. The first study is from Mountz *et al.* (11). They showed decreased blood flow in caudate nuclei and thalamus. In the second study, Kwiatek *et al.* (14) reported reduced blood flow into the right thalamus and inferior pontin tegmentum. There was no significant disturbance in blood flow of left thalamus and both caudate nuclei. Our results are quite different from these two studies. We showed significantly increased blood flow in both caudate nuclei. Decreased pons activity was observed which is similar to that of Kwiatek's (14) study. There was a decreased radioactivity uptake ratio in the pons, gyrus rectalis, right inferior temporal and right superior parietal cortex.

FM and chronic fatigue syndrome have similar clinical features and two recent functional neuroimaging studies investigating the related condition of chronic fatigue syndrome (32) have reported a reduction in activity within the pons

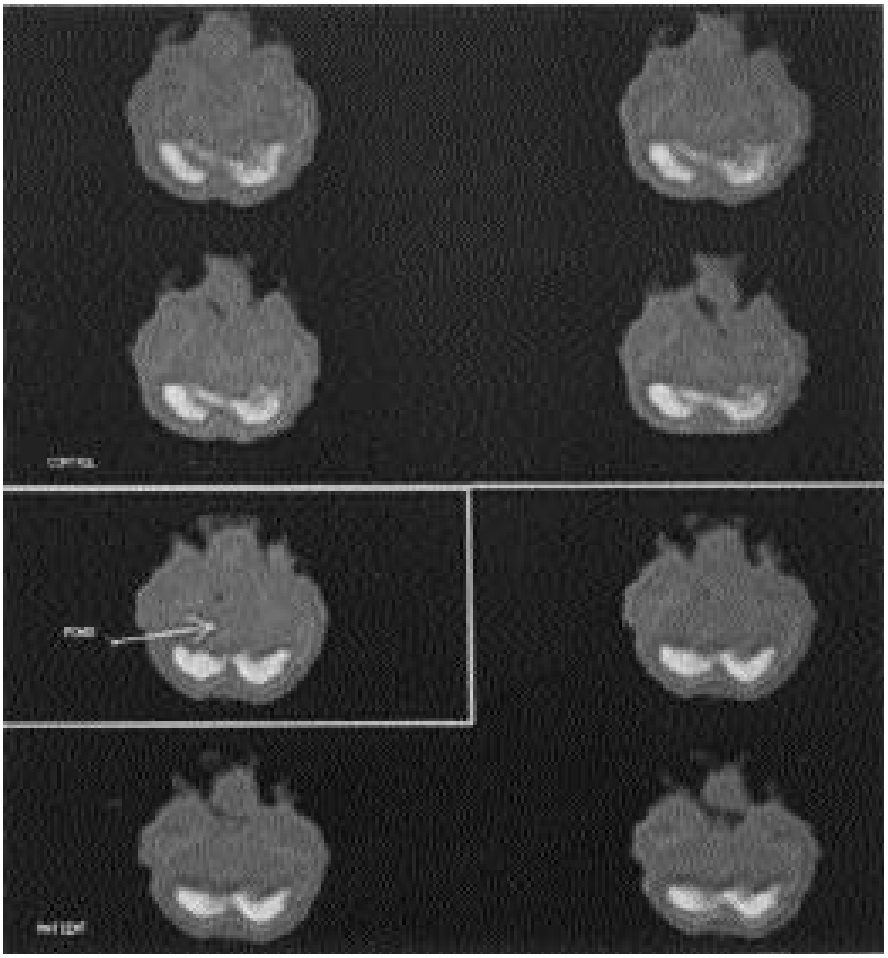

Fig. 3. Transverse sections of the brain SPECT, using Tc^{99m} - HMPAO of a patient with fibromyalgia and a normal control. There is a decreased blood flow in the pons in the patient with fibromyalgia comparing with normal subject.

(33, 34).

As reported in Mountz's (13) study, brief pain stimuli generated in the laboratory usually evoke increased rCBF to the thalamus and caudate nucleus (35,36) and Mountz *et al.* (13) have also reported that microtraumas to the muscle peripheral nociceptiv stimulus lead to increase in blood flow into the thalamus and caudate nuclei. However, longstanding and repeating stimulus results in compensatory reduction in brain perfusion. We found an increased blood flow in the caudat nuclei, which are related to pain modulation. One of the most important differences of our study was the mean age of patients and the duration of disease, which were low comparing with the values in the other studies.

An important point of our study is that we have evaluated 19 different cortical regions in addition to caudate nuclei, pons and both hemi thalamus. On the other studies researchers have especially concentrated on the regional blood flow in the caudate nuclei and thalamus as these regions are related with pain modulation. Cortical blood flow disturbances have firstly been evaluated in our study. Although the reason is not known, we have observed regional blood flow disturbances on the other areas of the brain as Kwiatek (14) has showed. We think it needs to use large patient population to explain these findings.

The limiting factor of our study is that we were not able to make MRI-SPECT co-registration. We, however, used normal brain morpho-functional reference atlas (20) to determine brain regions we interested in. In addition, MRI-SPECT co-registration generally has been absent in studies of patients with chronic pain, including those with rheumatic disorders (37). Also, within the power of our study, we were able to detect correlations between LCN and IL-2, between RSP and morning stiffness and sleep disturbance.

In summary, our study suggests that there is a significant difference in the rCBF and cytokines levels between patients and normal subjects. The rCBF in the caudate nuclei are increased and radioactivity uptake in the pons and some cortical regions are decreased in the young female patients with FM. IL 8 and IL 2r levels are also increased in these patients. Fibromyalgia patients with more mild depressive symptoms (i.e. HDRS-score < 16) have significantly lower serum IL 8 levels and more reduced regional blood flow in the pons than that of the patients who have more severe depressive symptoms (i.e. HDRS-score >16).

Our study has demonstrated some different results than other studies. We assume that this is due to the short duration of the disease and low mean age of patients in our study. Thus, the disease duration and mean age of study group must be taken account for the next investigation. In addition, we recommend carrying out these kinds of studies in a large patient population for clear understanding of aetiopathogenesis of fibromyalgia.

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