

Cytokine Levels in Fibromyalgia

Robert S. Katz, Rediet Kokebie; Rush University Medical Center, Chicago, IL

ABSTRACT

PURPOSE: Fibromyalgia (FMS) is usually considered as a non-inflammatory disease of unknown pathogenesis. However, studies on possible inflammatory or auto-immune mechanisms for development of FMS are lacking. Our aim was to compare the level of various cytokines/chemokines in patients with FMS as compared to other rheumatological conditions to explore inflammatory/auto-immune etiology of FMS.

METHODS: 20 patients with FMS and 10 active control patients were enrolled in an academic institute, Chicago, IL. The active control group had diagnosis of rheumatological disease other than FMS. FMS was diagnosed based on ACR classification criteria for FMS. Demographic and clinical information was obtained from all patients. Serum levels of following cytokine/chemokines were obtained by ELISA: Interleukin (IL)-1b (IL-1b), IL-1ra, IL-6, IL6r, IL-10, tumor necrosis factor (TNF- α), Matrix metalloproteinases-9 (MMP-9) and Vascular cell adhesion molecule (VCAM). Data was analyzed using Mann-Whitney ranksum test to compare the serum level of cytokines between 2 groups.

RESULTS: Our cohort had 20 FMS patients and 10 patients with other rheumatic disease control patients (Non-FMS). In the FMS group we had (16 females and 4 males). In the Non-FMS group there were 7 rheumatoid arthritis patients (5 females and 2 males), 1 female patient with systemic lupus erythematosus, 1 male patient with dermatomyositis, and 2 male patients with osteoarthritis (OA). The mean (SD) age of patients in FMS and Non-FMS groups were 48.7 years (11.8) and 55.9 years (13.7) respectively. Table 1 shows median values with inter-quartile range (IQR) for FMS and Non-FMS patients. The serum level of cytokines/chemokines IL-6, IL-10, and MMP-9 were significantly higher in patients with FMS as compared with Non-FMS. The level of IL-6R and VCAM were significantly lower in FMS as compared to Non-FMS group. The level of TNF- α , IL-1ra and IL-1b were not significantly different between the two groups.

TABLE 1. Median (IQR) levels of various cytokines/chemokines in patients with FMS and non-FMS.

	IL-1b pg/ml	IL-1ra pg/ml	IL-6 pg/ml	IL-10 pg/ml	TNF- α pg/ml	MMP-9 ng/ml	IL-6R pg/ml	hVCAM μ g/ml
FMS median (IQR)	2.2 (0.5-4.8)	104.5 (69.3-325.8)	9.5 (7.5-13.3)	1.5 (1-1.8)	4.4 (2.4-6.5)	190.1 (82.9-394)	5.2 (2.9-7.7)	1.92 (1.37-4.73)
Non-FMS Median (IQR)	0.4 (0.2-0.8)	119.4 (73.1-150.4)	3.9 (2.8-5.4)	0.6 (0.3-0.6)	6.1 (4.7-7)	36.6 (8.0-66.1)	2099 (95.9-3268)	10.7 (5.1-14.9)
P value	0.053(NS)	0.98(NS)	<0.001	<0.001	0.13(NS)	<0.001	<0.001	0.003

CONCLUSIONS: Fibromyalgia patients have elevated pro-inflammatory cytokines compared to normal, healthy controls. Cytokines in the CNS reflect immune activation. They may affect the activity of neurotransmitters and neurohormones, and play a role in producing the symptoms of fibromyalgia.

INTRODUCTION

The Fibromyalgia Syndrome (FMS) is usually considered as a non-inflammatory disease of unknown pathogenesis. Our aim was to compare the level of various cytokines/chemokines in patients with FMS as compared to other rheumatological conditions to explore a possible inflammatory/auto-immune etiology of FMS.

Others have reported cytokine abnormalities in fibromyalgia. Wallace et al. *Rheumatology* (2001) reported that patients with fibromyalgia had increases in serum levels of interleukin-6, interleukin-8 and interleukin-1 receptor antibodies. Interleukin-1 receptor antagonist (IL-1Ra) and Interleukin-6 (IL-6) were also significantly higher in stimulated and unstimulated peripheral blood mononuclear cells compared with controls.

Salemi et al. in the *Journal of Rheumatology* (2003) found elevated levels of interleukin-1a, interleukin-6, and tumor necrosis factor alpha in the skin of patients with fibromyalgia, using the reverse transcription polymerase chain reaction and immunohistochemistry.

Gur et al. in the *Journal of Rheumatology* (2002) described elevated levels of interleukin-8 in fibromyalgia. Interleukin-1 and interleukin-6 were not significantly elevated, but serum levels of interleukin-8, interleukin-2r were higher in patients with fibromyalgia than controls. Interleukin-8 levels were found to be related to pain intensity.

Maes et al. in *Psychoneuroendocrinology* (1999) described increased serum interleukin-6 and interleukin-1 receptor antagonist (IL-1ra) and lower serum CD-8 levels in fibromyalgia patients compared with healthy controls. Interleukin-6 receptor and interleukin-1Ra were significantly higher in fibromyalgia patients with increased depression scores, based on the Hamilton Depression Rating Scale.

PURPOSE

Fibromyalgia (FMS) is usually considered as a non-inflammatory disease of unknown pathogenesis. However, studies on possible inflammatory or auto-immune mechanisms for development of FMS are lacking. Our aim was to compare the level of various cytokines/chemokines in patients with FMS as compared to other rheumatological conditions to explore inflammatory/auto-immune etiology of FMS.

METHODS

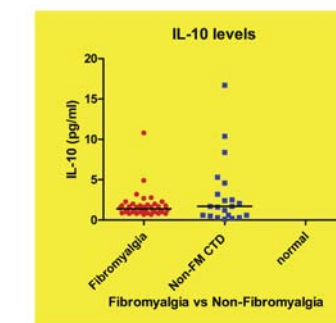
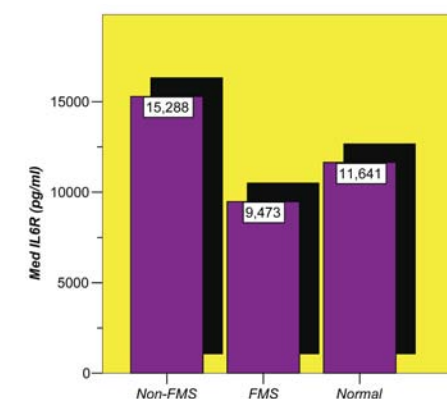
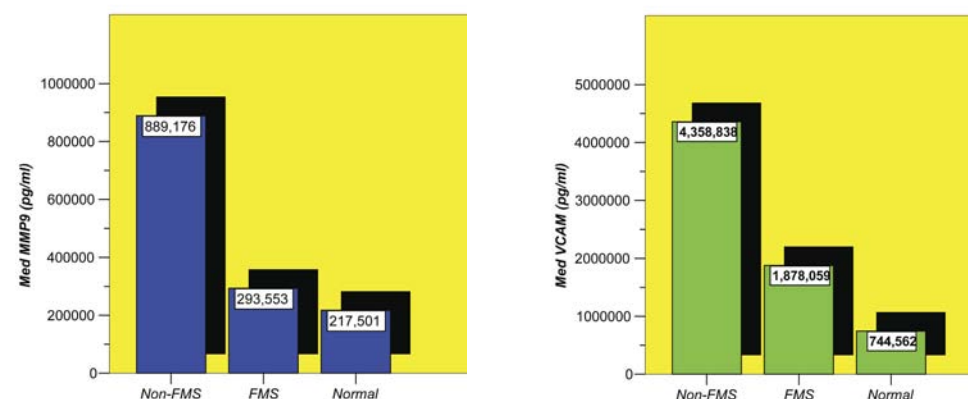
40 patients with FMS and 21 active control patients were enrolled in an academic institute, Chicago, IL. The active control group had diagnosis of rheumatological disease other than FMS. FMS was diagnosed based on ACR classification criteria for FMS. Demographic and clinical information was obtained from all patients. Serum levels of following cytokine/chemokines were obtained by ELISA: Interleukin (IL)-1b (IL-1b), IL-1ra, IL-6, IL6r, IL-10, tumor necrosis factor (TNF- α), Matrix metalloproteinases-9 (MMP-9) and Vascular cell adhesion molecule (VCAM). Data were analyzed using Mann-Whitney test to compare the serum level of cytokines between the two groups.

RESULTS

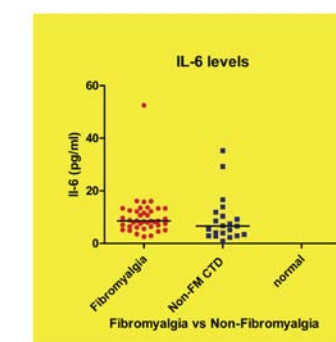
Our cohort had 40 FMS patients and 21 patients with other rheumatic disease control patients (Non-FMS). In the FMS group we had 35 females and 5 males. In the Non-FMS group there were x rheumatoid arthritis patients 7 females and 2 males), 3 female patient with systemic lupus erythematosus, 1 male patient with dermatomyositis, 4 male patients with osteoarthritis (OA), 1 female with sudden hearing loss, 1 female and 1 male with psoriatic arthritis (PSA), and 1 male with peripheral neuropathy. The mean (SD) age of patients in FMS and Non-FMS groups were 48.7 years and 55.9 years respectively. Table 1 shows the median values with ranges for FMS and non-FMS patients. The serum levels TNF- α , MMP-9, IL-6R, and VCAM were significantly lower in FMS patients. IL1-1b, IL-1ra, IL-6, and IL-10 were not significantly different between the two groups.

TABLE 1. Median (range) levels of various cytokines/chemokines in FMS and non-FMS patients

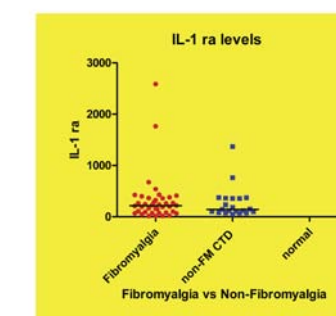
	IL-1b pg/ml	IL-1ra pg/ml	IL-6 pg/ml	IL-10 pg/ml	TNF- α pg/ml	MMP-9 ng/ml	IL-6R pg/ml	VCAM μ g/ml
FMS median (range)	0.2 (0.1-9.7)	217 (8-2588)	8.5 (2.6-52.5)	1.4 (0.7-10.8)	2.4 (0.4-16.0)	293553 (7105-1211428)	9473 (218-24672)	1878059 (618330-47448210)
Non-FMS Rheumatic Disease median (range)	0.2 (0.1-2.9)	143 (46-1368)	6.6 (0.9-35.3)	1.7 (0.1-16.7)	4.7 (1.2-12.9)	889176 (103806-7679524)	15288 (902-80614)	4358838 (614097-29289270)
P-value	0.99 (ns)	0.64 (ns)	0.092 (ns)	0.88 (ns)	0.035	< 0.001	0.002	0.008
Healthy Controls	1.5	134.8	4.6	4.1	5.9	3.22557	12405	826903



No difference in levels of IL-10 in two groups, P = NS. But IL-10 levels in Fibromyalgia and Rheumatic Disease Controls are significantly lower compared to normal healthy controls, p < 0.05



No significant difference in levels of IL-6 in both FMS and non-FMS groups, P = NS. Both groups were significantly higher than normal healthy controls, P < 0.05



No significant difference between the 2 groups. Both groups have significantly higher levels compared to healthy normal controls, P < 0.05

CONCLUSIONS

Cytokines in the CNS reflect immune activation and affect the activity of neurotransmitters and neurohormones. They could play a role in producing the symptoms of fibromyalgia.

FMS patients' pro-inflammatory cytokine levels are lower than those of non-FMS rheumatic disease controls. However, fibromyalgia patients have elevated pro-inflammatory cytokines compared to normal, healthy controls.