ORIGINAL ARTICLE

Differentiation between Primary fibromyalgia and Middle East Pain syndrome regarding Serum IL-6 level and MRI changes in hands and knees joints

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Abstract

Background: ***Fibromyalgia syndrome(FMS) is defined by the dysregulation of neuroendocrine function and/or nociceptive processing. Middle East Pain Syndrome(MEPS) is characterized by fibromyalgia that is accompanied by 2ry hyperparathyroidism and deficiency of vitamin D3.***

Aim: ***To differentiate between primary fibromyalgia and MEPS in terms of serum IL-6 level and MRI changes in the joints of the hands and knees.***

Patients and methods: ***This investigation involved forty cases diagnosed as MEPS and 40 patients with primary fibromyalgia. Full history taking, clinical examination, laboratory investigations involving vitamin D3, parathyroid hormone(PTH) and IL-6 serum levels, and MRI of both hand and knee joints.***

Results: ***Vitamin D3 levels decreased in both groups, with a significant reduction in the MEPS group in comparison with the FMS group. IL-6 levels increased in both groups without significant differences, but correlated with clinical severity scores. PTH levels were significantly greater in the MEPS group (p-value less than 0.001). Hand MRI showed more spur excrescences and degenerative changes in the MEPS group(p-value less than 0.05). Knee MRI revealed higher chondrocalcinosis in the MEPS group, increasing with age and disease duration, while synovial hypertrophy showed no significant difference.***

Conclusion: ***Vitamin D3 serum level decreased in both MEPS and FMS cases, significantly decreasing in the MEPS group compared to the FMS group, necessitating assessment and correction. IL-6 serum level increased in both groups with an insignificant difference; it positively correlates with clinical manifestations. MRI showed increased chondrocalcinosis and degenerative changes in MEPS patients.***

Keywords: Primary fibromyalgia; Middle East Pain syndrome; Serum IL-6 level; MRI changes

1. Introduction

FMS is defined by a dysregulation of neuroendocrine function and/or nociceptive processing. Its clinical manifestations involve global,[1] widespread pain that is frequently accompanied by a sleep disturbance and symptoms that indicate autonomic dysfunction,[2] like irritable bowel syndrome and interstitial cystitis.[3] Osteoporosis or osteopenia can result in bone pain because of hyperparathyroidism, which is caused by the persistent elimination of calcium and bleeding within the bone. Calcium pyrophosphate deposition may lead to a variety of conditions, including pseudogout, chondrocalcinosis, joint laxity and muscle atrophy, and degenerative arthritis .[4] There are numerous FM cases that are related to a combination of bilateral wrist and hand arthritis, vitamin D3 deficiency, and an elevated serum PTH concentration. They have been misdiagnosed as having either seronegative or seropositive RA, which led to the failure of therapy and long-term pain. The cases were diagnosed with a novel syndrome known as MEPS by Elbeialy et al.,[5] due to the fact that all of the cases were from the Middle East.[6,7]

This investigation aimed to differentiate between primary FMS and MEPS as regards serum IL-6 level and MRI changes in hands and knees joints.

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2. Patients and methods

This comparative investigation has been carried out on forty cases diagnosed as MEPS; there were four men (ten percent) and thirty-six women (ninety-five percent), and their illness duration ranged from one to five years. In addition, forty FM stations were involved in the comparison. The patient population consisted of one man (2.5%) and forty-nine women (97.5%). The patients' ages ranged from eighteen to forty-five years, and the illness durations ranged from one to six years. Cases have been recruited from the outpatient clinic of the rheumatology and rehabilitation department at Al Zahraa University Hospital between January 2023 and February 2024. All cases have been recruited.

Methods

All patients have been subjected to:

Clinical evaluation: History taking, clinical and musculoskeletal examination, widespread pain index (WPI), symptom severity scale (SSS), and the number of tender points have been determined, and disease severity by VAS from 0 to 10.

The diagnosis of FMS was based on the 2016 modified ACR Diagnostic Criteria for FM. A patient is considered to have FM if 3 of the following conditions are met:

(1) WPI≥ 7 and SSS score ≥ 5 or WPI of 4–6 and SSS score ≥ 9.

(2) Generalized pain, defined as pain in at least 4 out of 5 regions, must be present. Jaw, chest, and abdominal pain are not included in the generalized pain definition.

(3) Symptoms have been generally present for at least 3 months.

(4) A diagnosis of FM is valid irrespective of other diagnoses.[8]

The MEPS cases were diagnosed in accordance with Elbeialy et al.,[5]. Other rheumatic illnesses, such as psoriatic arthritis, erosive OA, RA, viral arthritis, IBD arthritis, reactive arthritis, Lyme's illness, or palindromic rheumatism, as well as systemic illnesses like cardiovascular, renal, neurologic, metabolic, and pregnant or breastfeeding females, have been excluded from the investigation.

Laboratory evaluation: Routine laboratory investigations, 1, 25 cholcalciferol, PTH, and IL-6 serum levels. We used the kits for serum IL-6 ELISA Kit (BT LAB Bioassay Technology Laboratory Cat No E0082Hu) and analyzed them using the Sandwich ELISA Detection technique. Sampling: Blood allowed to clot for ten to twenty minutes at room temperature, centrifuged at 2000-3000RPM for twenty minutes, and the supernatant was collected without sediment.

Assay principle: A plate coated with antibodies has been used to add Human IL-6 antibodies to the reagent, which was an Enzyme-Linked Immunosorbent Assay. Streptavidin-HRP is followed by biotinylated human IL-6 antibody and the sample's IL-6, which binds to the antibodies. The unbound Streptavidin-HRP is removed following incubation, and a substrate solution is introduced. In direct proportion to the quantity of human IL-6, the pigmentation develops. An acidic stop solution has been utilized to terminate the reaction, and the absorbance has been determined at 450 nanometers. Precision: Precision within an assay (intra-assay precision). In order to evaluate intra-assay precision, three samples of known concentration have been analyzed on a single plate. The inter-assay precision (precision between assays) was evaluated by testing three samples of known concentration in separate assays. The CV% was calculated as SD/mean × 100, with an intra-assay CV of under eight percent and an inter-assay CV of under ten percent.

Plain X-ray of hands for detection of subperiosteal bone resorption, terminal tuft erosions (acro-osteolysis), and spur-like excrescences present in MEPS. MRI of hands and knees was done for all patients. MRI sequences have been utilized, like turbo spin echo sagittal proton density, T1 and T2 weighted images, coronal STIR, and axial T2 weighted images. Degenerative changes of the knees and hand joints: include focal loss of articular cartilage, osteophytes, erosions, chondrocalcinosis, subchondral marrow lesions, effusion, synovial hypertrophy, and muscle and tendon disorders: Strains, complete and partial tears, and tendonitis.

Statistical analysis

The Statistical Program for Social Science (SPSS) version 24 has been utilized to analyze the data. Frequency and percentage were the metrics utilized to represent qualitative data. The quantitative data have been presented as the median (IQR) due to the non-normal distribution of the data. Median: The median is determined by arranging all data points and selecting the one in the middle (or, in the event that there are two middle numbers, by calculating the mean of the two). The inter-quartile range (IQR) is a statistical dispersion metric that quantifies the diversity of the data. It is defined as the variance between the 75th and 25th percentiles of the data. The independent sample T test, Chi-square test, Pearson's correlation coefficient (r), and Probability (P-value) have been conducted. A P-value of less than 0.05 has been deemed significant, a P-value of less than 0.001 has been deemed highly significant, and a P-value of more than 0.05 has been deemed insignificant.

3. Results

Patients of MEPS & FMS showed insignificant variance among them with regard to age, sex and disease duration, p-value more than 0.05, table (1).

Table 1. Comparison of general characteristics between MEPS and FMS groups:

		MEPS (NUMBER = 40)	FMS (NUMBER = 40)	STAT. TEST	P-VALUE
AGE (YEARS)	Mean ±SD	38.3 ± 7.9	36.2 ± 8.6	T = 1.13	0.260
	Range	21 - 50	20 - 50		
SEX	Male	4 10%	1 2.5%	X^2 = 1.92	0.166
	Female	36 90%	39 97.5%		
DISEASE DURATION (YEARS)	Mean ±SD	2.9 ± 1.2	3.3 ± 1.7	T = 1.21	0.230
	Range	1 - 5	1 – 6		

. S: p-value less than 0.05 considered significant. X2: Chi-square test. NS: p-value more than 0.05 considered non-significant.

Number of tender points, WPI, SSS and VAS revealed statistically insignificant variance between MEPS & FMS groups, p-value more than 0.05, table (2).

Table 2. Comparison among investigated groups regarding clinical data.

		MEPS (N = 40)	FMS (N = 40)	T	P-VALUE
NO OF TENDER POINTS	Mean ±SD	14.6 ± 1.8	14.4 ± 2.4	0.26	0.792
	Range	12 - 18	11 - 18		
WPI	Mean ±SD	11.6 ± 2.4	11.1 ± 3	0.89	0.371
	Range	9 - 17	8 - 17		
SSS	Mean ±SD	5.6 ± 1.2	5.4 ± 0.9	0.75	0.451
	Range	5 - 9	5 - 8		
VAS	Mean ±SD	7.6 ± 1.2	7.5 ± 1.6	0.55	0.578
	Range	6 - 10	5 - 10		

A highly significantly decreased Vitamin D level and significantly increased PTH level in MEPS group compared with FMS group. Vitamin D status showed significant increased percentage of vitamin D deficiency in MEPS group when compared with FMS group, (p-value = 0.001). IL-6 levels increased in both groups with insignificant variance. Also, ESR and Hb levels revealed insignificant variance among groups. (Table 3)

Table 3. Comparison of laboratory data among studied groups:

		MEPS (N = 40)	FMS (N = 40)	TEST	P-VALUE
VITAMIN D LEVEL (NG/ML)	Median	10	20	T = 7.76	< 0.001
	IQR	8 - 11.8	14.3 - 28.8		
VITAMIN D STATUS	Deficient	40 100%	30 75%	X^2 = 11.4	0.001
	Normal	0 0%	10 25%		
HB (G/ DL)	Median	12	12	T = 1.7	0.092
	IQR	11 – 12	11.3-13		
PTH (PG. / ML)	Median	100	40	T = 8.85	< 0.001
	IQR	60 - 167.5	30 – 50		
ESR (MM/HR)	Median	23.5	24	T = 1.06	0.288
	IQR	20 – 27	22 – 28		
IL-6 (PG. / ML)	Median	30.3	32.1	T = 0.16	0.868
	IQR	21.4 -47.1	20.2 – 47.9		

A significant increased spure excrescences in all MEPS group (100%) when compared with FMS group (0 patients, 0%) by plain x-ray and MRI studying. Wrist and hands MRI results showed that, degenerative changes significantly increased in MEPS group in 19 patients (47.5%) when compared with FMS group in 10 patients (25%). Synovial hypertrophy also increased in MEPS group in 16 patients (40%) compared with FMS group in 10 patients (25%) but with insignificant variance. (Table 4)

Table 4. Comparison of MRI results of wrist & hands between studied groups.

WRIST & HANDS MRI		MEPS (N = 40)		FMS (N = 40)		TEST	P-VALUE
SPURE EXCRESCENCES	No	0	0%	40	100%	X^2 = 80	< 0.001 HS
	Yes	40	100%	0	0%		
DEGENERATIVE CHANGES	No	21	52.5%	30	75%	X^2 = 4.3	0.036 S
	Yes	19	47.5%	10	25%		
SYNOVIAL HYPERTROPHY	No	24	60%	30	75%	X^2 = 0.24	0.622 NS
	Yes	16	40%	10	25%		

Knee MRI results revealed a high significant increased chondrocalcinosis in MEPS group, it was found in 14 patients (35%), while no chondrocalcinosis was present in FMS group (0%). Degenerative changes were increased in MEPS group which present in 17 patients (42.5%) versus 11 patients (27.5%) in FMS group but with no significant difference. (Table 5)

Table 5. Comparison of knee MRI results between studied groups.

KNEE MRI		MEPS (N = 40)		FMS (N = 40)		TEST	P-VALUE
CHONDROCALCINOSIS	No	26	65%	40	100%	X^2 = 16.9	< 0.001
	Yes	14	35%	0	0%		
DEGENERATIVE CHANGES	No	23	57.5%	29	72.5%	X^2 = 1.97	0.160
	Yes	17	42.5%	11	27.5%		

In MEPS group, IL-6 serum level showed high significant positive correlation with No. of tender points, WPI, SSS, VAS and PTH level with r = 0.57, 0.57, 0.63, 0.6 and 0.39 respectively, while significant negative correlation with vitamin D (p-value = 0.018, r = - 0.37). IL-6 didn't correlate with ESR, Hb, age or disease duration (p-value = 0.397, 0.06, 0.199 & 0.653 and r = - 0.14, 0.3, 0.2 & 0.73) respectively. (Figure 1)

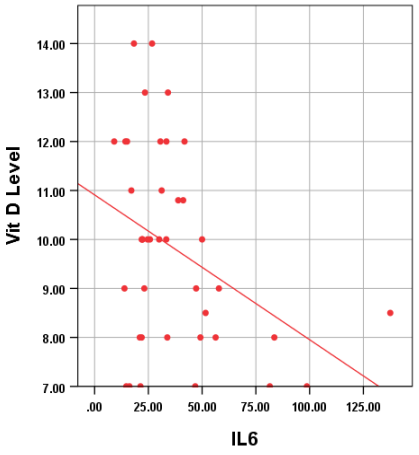

Figure 1. Negative association between IL-6 and vitamin D in MEPS group.

In FMS group there were non-significant positive

association between IL-6 and No. of tender points, WPI, SSS, VAS, serum vitamin D3, PTH, Hb and age with r = 0.21, 0.18, 0.15, 0.22, 0.14, 0.2, 0.08, and 0.112 respectively. It also showed non-significant negative correlation with ESR & disease duration with r = 0.08 & 0.18 respectively, while it didn't correlate with degenerative changes, chondrocalcinosis &synovial hypertrophy in MRI results in both groups. (Figure 2)

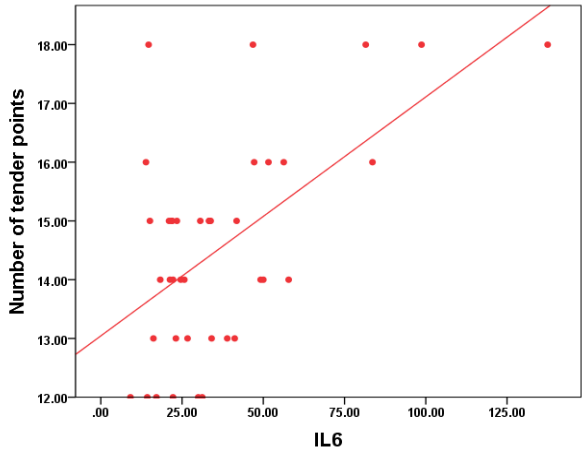

Figure 2. Positive association between IL-6 and No of tender joints in MEPS group.

4. Discussion

According to Elbeialy et al,[5] MEPS is defined as FMS associated with bilateral hand and wrist arthritis, deficiency of vitamin D3, and elevated serum PTH level. Serum 1, 25(OH)D is considered deficient when the level is below 20 ng/ml.[9] The normal range of PTH in blood is from 15 to 65 pg./ml.[10] Results of this study showed that, in spite of deficient median Vit. D3 serum level in the FMS group, a highly significant decrease in median vitamin D serum level, and a highly significant increase in median PTH level in the MEPS group, compared with the FMS group, which is within the normal median level for PTH.

These findings are consistent with the investigation conducted by Elbeialy et al,[5] on 400 FM patients who attended outpatient clinics at Al-Azhar University Faculty of Medicine Hospitals in Egypt and Elaj specialized clinics in Saudi Arabia between November 2014 and December 2019. They observed that all MEPS cases had vitamin D3 insufficiency or deficiency, and up to seventy-five percent of these cases had elevated PTH levels. Restricted sun exposure as a result of cultural practices, dress styles, limited time spent outdoors, and protracted breastfeeding without supplemental vitamin D are potential etiologies of vitamin D3 shortage in the Middle East, regardless of the abundance of sunshine.10 The level of IL-6 in the circulation is approximately between one and five picograms per milliliter under normal conditions.[12]

Our results showed increased median IL-6 serum level in MEPS and FMS groups with no significant difference. IL-6 level gives a highly significant positive correlation with the number of tender points, WPI, SSS, and VAS in both groups. These outcomes are consistent with the results of Canpolat et al,[11], who discovered a statistically significant positive association between VAS and IL-8 serum concentrations in FM cases. This outcome supports the hypothesis that the severity of pain may be influenced by elevated proinflammatory cytokine concentrations through raising the number of tender points, WPI, SSS, and VAS, leading to hyperalgesia in these cases.

Wrist & hands MRI results revealed a high significant increased percentage of spure execresens and increased percentage of degenerative changes in MEPS group when compared with FMS group. Also, significant increased percentage of degenerative changes and synovial hypertrophy in MEPS group with older ages and long disease duration and female sex when compared with FMS group.

These outcomes are in accordance with the findings of Elbeialy et al.[5], who documented the existence of tuft spurs-like excrescences in the distal phalanx of fingers, primarily the thumb, in MEPS cases. These excrescences resemble the "spade phalanx sign" of acromegaly, as demonstrated by x-ray. They additionally described degenerative alterations to the wrist and hand, including subchondral osteopenia of the proximal and middle phalanges, mild subperiosteal resorption along the radial aspect of the middle phalanx, ulnar styloid resorption, and radiocarpal and scapho-trapezoid joint arthritis. The resorption was primarily affecting the thumbs.

Our outcomes supported by Freitas et al.[13] as they stated d that, hands radiographs may yield the diagnostic finding of subperiosteal resorption.

MRI findings of knee joints showed a highly significant increase in the percentage of chondrocalcinosis in 14% of the MEPS group with increased age and long disease duration when compared with the FMS group (0%). While statistically insignificant variance between MEPS and FMS regarding degenerative changes, the results showed an increased percentage of degenerative changes in MEPS patients when compared with the FMS group, with increased age and long disease duration in both groups.

These results were in accordance with the investigation carried out by Elbeialy et al.,[5] who found chondrocalcinosis in 70%, intracortical resorption, in MEPS patients by x-ray imaging.

Also, Dzekan et al.[11] and Mahgoub Met al.[14] in their studies found increased frequency of knee osteoarthritic degenerative changes among cases with FMS compared with healthy controls.

4. Conclusion

The outcomes of this investigation confirmed a severe deficiency in vit D and increased PTH in MEPS patients compared to FMS patients. It also showed an increased IL-6 above the normal levels in both diseases, more in MEPs patients which correlated with clinical disease severity. MRI findings showed increased chondrocalcinosis and degenerative changes, and slightly increased synovial hypertrophy in MEPs compared to FMS patients.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

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