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ORIGINAL ARTICLE

An increased prevalence of fibromyalgia in iron deficiency anemia and thalassemia minor and associated factors

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Abstract In this study, we evaluated the prevalence of fibromyalgia (FM) in iron deficiency anemia (IDA) and thalassemia minor (TM) patients and associated factors. In addition, we investigated the prevalence of IDA in outpatients with fibromyalgia, and its effect on clinical findings. The study included 205 IDA, 40 TM patients and 100 healthy controls. FM was diagnosed according to 1990 ACR criteria. Whole blood count, biochemical tests, and serum iron parameters were determined. Pain, fatigue, and FM Impact Questionnaire (FIQ) functional item scores were assessed in FM subjects. In addition, the prevalence of IDA in FM patients diagnosed at the Rheumatology Outpatient Clinic was determined. The prevalences of FM in IDA (17.6%) and TM (20%) groups were higher than in controls (6%; p values 0.006 and 0.025, respectively). When IDA patients with FM were compared to those without FM, it was seen that a higher percentage were females, married, and a higher percentage had history of pica (all p values<0.05). Serum hemoglobin and iron parameters did not differ between IDA patients with and without FM. IDA was detected in 48 (24.5%) of 196 FM patients. FM patients without IDA had higher sleep disturbance scores ($p=0.012$) and longer duration of FM ($p=0.045$). FM was a common finding in patients with IDA and TM. FM was associated with female sex and history of pica in IDA patients, and not associated with serum hemoglobin and selected iron parameters. The presence of FM in TM had no association with any of the above-mentioned parameters.

Keywords Chronic widespread pain · Fibromyalgia · Iron deficiency anemia · Thalassemia minor

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Introduction

Fibromyalgia (FM) is a chronic pain syndrome and it is characterized by diffuse pain and tenderness of specific points on examination [1]. FM affects primarily females, and when American College of Rheumatology (ACR) criteria are used, its prevalence in developed nations varies between 0.5% and 4% [2]. According to ACR criteria for FM, an individual must have both a history of chronic widespread pain involving all four quadrants of the body and the presence of 11 of 18 "tender points" on physical examination. The exact pathogenesis of FM is unknown. It is known that the prevalence of the diseases is higher in rheumatic diseases like rheumatoid arthritis (RA), systemic

lupus erythematosus (SLE), Sjögren's syndrome, osteoarthritis (OA), and Behçet's disease [3]. Furthermore, it was reported that the prevalence of FM was increased in chronic diseases like diabetes mellitus [4].

Iron deficiency anemia (IDA) is a common disorder with many adverse consequences like decreased work and exercise performance, immune system abnormalities, and neurologic dysfunction [5]. There are studies which reported that adolescents with IDA had cognitive dysfunction which improved after iron supplementation [6, 7]. The thalassemias, the commonest monogenic diseases, are a heterogenous group of inherited disorders of hemoglobin synthesis. They occur at a high frequency throughout parts of Africa and the Mediterranean region, the Middle East, the Indian subcontinent, and Southeast Asia [8].

FM-related symptoms like fatigue and cognitive dysfunction are also quite common in IDA and TM. From a clinical point of view, it is important to understand the association between FM and IDA and also TM. Until now, the prevalences of FM in IDA, thalassemia minor, (TM) and the influences of IDA, TM on FM have not been evaluated. In our study, we searched for the prevalences of FM in IDA, TM patients and determined factors associated with the presence of FM. In addition, we investigated the prevalence of IDA in FM patients and evaluated its effect on the clinical findings of FM.

Materials and methods

We included 205 consecutive IDA patients and 40 TM patients who were admitted to our Internal Medicine Outpatient Clinic between 2003 and 2005. In addition, 196 patients diagnosed with FM at the Rheumatology Outpatient Clinic at the same time period were included. One hundred healthy subjects (89 females, 11 males, mean age: 38.5±12.4 years) who were hospital personnel (physician, nurse, laboratory worker) were taken as the control group. All of the subjects were Turkish and have been residing in the Thrace region which is in northwestern Turkey. Subjects with a known malignancy and those with an acute or chronic infection, chronic renal and liver failure were excluded. All patients were told the study design and all gave verbal consent to participate in the study.

Each patient was interviewed to determine his/her demographic and clinical features, including age, marital status, educational level, smoking and alcohol intake, and menopausal status; and specific questions regarding rheumatic symptoms were asked. A fasting venous blood sample was obtained from IDA and TM patients to determine whole blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and standard parameters of iron status. Whole blood counts were determined using the CellDyn 3700 analyzer; and hemoglobin (Hb), mean corpuscular volume (MCV), red cell distribution width (RDW), hematocrit and platelet values were recorded down. ESR was determined by the Westergren method, and CRP by the nephelometric method. Serum iron (SI; normal range for males: 31–144 μg/dl, and for females: 25–156 μg/dl) and unsaturated iron binding capacity (UIBC; *N*: 110–370 μg/dl) were analyzed with spectrophotometric methods by the instrument ARCHITECT c8000 System (Abbott Laboratories, Diagnostics Division, IL, USA). Total iron binding capacity (TIBC) was obtained by adding SI and UIBC. Transferrin saturation (TS) was calculated from the equation: (SI/TIBC)×100%. Serum ferritin (SF) was determined with a chemiluminescence immunometric assay on the IMMULITE 1000 analyzer (Diagnostic Products Corporation, DPC, LA, USA). Normal ranges for ferritin concentration were 28–397 ng/ml for adult men and 6–159 ng/ml for women.

IDA was defined as hemoglobin serum concentration of less than 13.5 g/dl in men (normal male adult 13.5–17.5 g/dl) or less than 12 g/dl in women (normal female adult 12.0–15.5 g/dl) with SF less than 12 ng/ml, low SI, raised TIBC, and TS<16%. High-performance liquid chromatography (HPLC) Hb electrophoresis was carried out in all the patients with MCV<76 fl: subjects with an HbA2>3.5% were diagnosed with TM.

In all subjects, a count of 18 tender points at nine symmetrical sites was performed by thumb palpation. During tender point examination, one rheumatologist applied a uniform, manual finger pressure, until the fingernail bed blanched, at each of the nine paired anatomical locations. If some involuntary verbal or facial expression of pain occurred, definite tenderness of any of the points was considered to be present. The tender point count was calculated by summing up the number of tender points. Thumb palpation was also performed at four control sites, and patients were not told which were the tender or control points [9]. All tender point examinations were performed by the same observer (Ömer Nuri Pamuk).

Subjects were diagnosed as having FM if they fulfilled the ACR 1990 criteria [10]: widespread pain for >3 months and tenderness of 11 or more specific tender points. Chronic widespread pain (CWP) was defined as pain >3 months in at least two contralateral quadrants in the axial skeleton. Current pain and fatigue were determined in patients who fulfilled the criteria for FM by using a visual analogue scale between 0–10, featuring 10 as the worst possible condition. All of the FM patients were administered the physical function items of the FM Impact Questionnaire (FIQ) score [11]. The responses of FIQ were scaled from 0 = "always able to do" to 3 = "never able to do". The FIQ is a 10 component, 19-item questionnaire developed to assess the influence of FM on various health

Table 1 The characteristics of IDA and TM patients included into the study

	IDA	TM	p
N (F/M)	205 (186/19)	40 (31/9)	0.027
Age (mean±SD; years)	40.5±13.5	40.1±12.3	NS
Education (>9 years), *n* (%)	87 (42.4)	11 (27.5)	NS
Marital status (married), *n* (%)	159 (77.6)	28 (70)	NS
Menopause, *n* (%)	18 (9.7)	5 (16.7)	NS
Smoking, *n* (%)	64 (31.2)	10 (25)	NS
Alcohol, *n* (%)	20 (9.8)	6 (15)	NS
Hemoglobin (g/dl)	9.3±1.6	10.7±1.3	<0.001
Hematocrit (%)	29.3±4.3	33.3±4	<0.001
MCV (fl)	69.5±7.4	64.2±3	<0.001
RDW (%)	18±4.2	16.8±3.8	0.15
Platelets ($\times 10^9$/l)	310.1±94.5	270.4±77	0.015
Iron (μg/dl)	25.1±14	98.7±35.5	<0.001
Total iron binding capacity (μg/dl)	403.6±45	302.9±46.9	<0.001
Ferritin (ng/ml)	3.8±2.3	114.5±181	0.001
ESR (mm/h)	18.9±16	7.2±5.4	<0.001
CRP (mg/dl)	0.51±1.2	0.48±0.4	NS

NS Not significant

dimensions. Sarmer et al. [12] performed the Turkish validation and reliability of the FIQ score.

Chi-square test was used to compare categoric variables. In the comparison of quantitative variables, unpaired *t*-test was used. Correlation analyses were performed by Pearson's test.

Results

Characteristics of IDA and TM patients in our study are seen in Table 1. The control group was age and sex matched with the patient groups. The age distributions of the groups were not different; however, the ratio of females in the IDA group was higher than that in the TM group (22.5% vs. 9.3%, $p=0.027$). In the IDA group, Hb, hematocrit, SI, and SF concentrations were significantly lower than in the TM group; MCV, platelets, TIBC and ESR levels were significantly higher in comparison to TM (Table 1). FM was diagnosed in 36 patients (all females) with IDA (17.6%), eight patients (seven females, one male) with TM (20%) and six patients (all females) in the control group (6%). The prevalences of FM in IDA and TM patients were significantly higher than in the control group (p values 0.006 and 0.025, respectively).

The comparison of the clinical features of IDA patients with and without FM is seen in Table 2. In the IDA with FM group, the percentages of females, married, parous subjects, and subjects with a history of pica were higher than those in the IDA group without FM (all p values <0.05).

Table 2 The comparison of the general features of IDA patients with and without FM

	IDA with FM	IDA without FM	*p*
N (%)	36 (17.6)	169 (78.7)	
Female, *n* (%)	36 (100)	150 (88.8)	0.029
Age (mean±SD; years)	40.9±12.1	40.4±13.8	NS
Education (>9 years), n (%)	12 (33.3)	75 (44.4)	NS
Marital status (married), n (%)	33 (91.7)	126 (74.6)	0.025
Smoking, *n* (%)	12 (33.3)	52 (30.8)	NS
Alcohol, *n* (%)	3 (8.3)	17 (10.1)	NS
Birth history, *n* (%)	29/30 (96.7)	102/146 (69.9)	0.009
Pica history, *n* (%)	9/30 (30)	21/165 (12.7)	0.025
Menopause, *n* (%)	2/36 (5.6)	16/150 (10.7)	NS
Hemoglobin (g/dl)	9.6±1.2	9.2±1.7	NS
Hematocrit (%)	30.1±3.1	29.1±4.5	0.09
Platelets ($\times 10^9$/l)	331.4±86.7	306.3±95.8	NS
Iron (μg/dl)	24.6±12	25.2±14.5	NS
Total iron binding capacity (μg/dl)	407.7±49	400±46.8	NS
Ferritin (ng/ml)	4.5±2.9	3.7±2.2	NS

NS Not significant

Table 3 The comparison of the characteristics of IDA with FM patients to those of TM with FM, controls with FM, and FM outpatients

	IDA with FM	TM with FM	Controls with FM	FM outpatients
N (%)	36 (17.6)	8 (20)	6 (6)	196
Female, *n* (%)	36 (100)	7 (87.5)	6 (100)	187 (96.6)
Age (mean±SD; years)	40.9±12.1	43.1±10.9	33.5±6	42.2±11.4
CWP severity (0–10)	3.9±1.5	4.1±2	5.5±1.4	5.6±1.9*
Fatigue (0–10)	4.3±2.3	3.6±1.9	5±2.5	5.4±2.6**
FIQ funct. item (0–3)	1.1±0.76	0.83±0.6	0.95±0.9	1.27±0.7

FM outpatients are different from IDA with FM and TM with FM groups
*$p<0.001$, **$p<0.05$

In addition, in the IDA with FM group, hematocrit level tended to be nonsignificantly higher than the others ($p=0.09$; Table 2). There were no significant differences between TM patients with and without FM (data not shown).

The characteristics of IDA and TM patients with FM, healthy control group with FM and patients diagnosed with FM at the Rheumatology Outpatient Clinic are seen in Table 3. Age and sex distribution of FM patients in four of these groups were similar. The fatigue score in FM outpatients was significantly higher than IDA patients with FM and also TM patients with FM (p values<0.05). The CWP severity score in FM outpatients was significantly higher than only IDA patients with FM ($p<0.001$).

When FM patients attending the Rheumatology Outpatient Clinic were evaluated, it was seen that 48 (24.5%) of them had IDA. When FM patients with IDA were compared to those without IDA, it was found that the latter group had a higher sleep disturbance score ($p=0.012$), and a longer duration of FM ($p=0.045$). Although the mean age and the percentage of patients who used alcohol were higher in the FM group with IDA, the difference was not significant ($p>0.05$). The comparison of characteristics of FM patients with and without IDA diagnosed at the Rheumatology Outpatient Clinic is seen in Table 4.

Discussion

In our study, we detected an increased prevalence of FM in IDA and TM patients when compared to controls. Our study was the first to investigate the frequency of FM in IDA and TM. It was suggested that there was an association between hemoglobin level and cognitive function in IDA patients [7]. In addition, fatigue, inability to concentrate, and other nonspecific symptoms have been often attributed to iron deficiency, although the evidence to support this association is not strong [13]. There are studies which reported that nonspecific symptoms regressed after iron replacement therapy [14, 15]; however, there are conflicting results [6, 16]. Consequently, nonspecific symptoms in patients with IDA are generally thought to be primarily associated with anemia. Nevertheless, when we consider the results of our study, we might suggest that the increased

Table 4 The comparison of the general features of FM patients with and without IDA who are being followed up at our Rheumatology Outpatient Clinic

	FM with IDA	FM without IDA	*p*
N (%)	48 (24.5)	148 (75.5)	–
Female, *n* (%)	44 (91.7)	143 (96.6)	NS
Age (mean±SD; years)	39.9±11.1	42.9±11.4	0.1
FM duration (years)	4.1±4.4	5.8±6.5	0.045
Education (>9 years), *n* (%)	30 (62.5)	79 (53.4)	NS
Marital status (married), *n* (%)	41 (85.4)	135 (91.2)	NS
Smoking, *n* (%)	12 (25)	45 (30.4)	NS
Alcohol, *n* (%)	3 (6.3)	2 (1.4)	0.09
Menopause, *n* (%)	13 (28.3)	57 (39.9)	NS
CWP severity (0–10)	5.28±2.1	5.7±1.8	NS
Fatigue severity (0–10)	3.6±1.2	3.7±1.2	NS
Sleep disturbance (0–10)	2.6±1.3	3.1±1.3	0.012
FIQ functional item score (0–3)	1.23±0.8	1.27±0.7	NS

NS Not significant

frequency of FM in IDA and TM might contribute to a great extent to an important proportion of nonspecific symptoms.

There was a higher percentage of females, married, and parous patients in the IDA group with FM group when compared to the IDA group without FM. Most of the studies about the prevalence of FM in both the general population and in specific diseases reported that it was more common among females [4]. An interesting finding in the IDA with FM group was that the percentage of patients with pica was higher in this group. One of the symptoms of IDA might be pica. Pica could be a spectrum of obsessive–compulsive disorder or reminiscent of an impulse control disorder [17]. It was stated that approximately one third to two thirds of FM patients had anxiety or depression [18]. As a result, when patients with pica define nonspecific symptoms, the possibility of FM should initially come to mind.

Except for a nonsignificantly higher level of hematocrit in the IDA group with FM when compared to the IDA group without FM, serum iron parameters in both groups were similar. Therefore, the increased prevalence of FM in IDA is not directly associated with the changes of serum iron and blood count parameters.

Our results revealed that FM outpatients had higher fatigue scores than IDA and TM patients with FM. Nevertheless, pain scores of FM outpatients were significantly higher than only IDA patients with FM. It is an expectable result that pain and fatigue scores in FM patients diagnosed among subjects seeking medical care for their CWP are higher than in patients with IDA who are found out to have FM. In our study, the prevalence of FM in TM was increased. Although the number of patients is not much, FM in TM has been evaluated for the first time. In our search of the literature, we cited data about nine FM patients who had sickle cell anemia.

We diagnosed that nearly one fourth of FM patients attending the Rheumatology Outpatient Clinic had IDA. FM patients without IDA had a higher sleep disturbance score; their pain, fatigue and FIQ scores were not different. We might conclude that IDA is common in FM patients; however, it does not have any serious effect on symptoms other than sleep disturbance. The presence of restless leg-associated sleep disturbance in FM and its association with FM is known [19, 20]. Nevertheless, none of our FM patients had restless leg.

Previous studies reported that neurotransmitters in the brain were altered due to hypoxia in IDA and thalassemia [21]. In addition, iron is present in the structures of enzymes which play a role in the production of important neurotransmitters like serotonin, norepinephrine; and, in IDA, this production might be impaired [21]. In FM, similar to the condition in IDA, noradrenaline in CSF and serotonin and its precursors in both serum and CSF were found to be decreased [22]. These findings support the increased prevalence of FM in IDA. In addition, in IDA there are important changes in muscle metabolism and energy use; and exercise performance becomes worse [23].

Our study had some limitations. First, we did not evaluate parameters like anxiety–depression which affect the presence of FM in IDA. Second, we did not follow up the longitudinal change on the presence of FM and its symptoms after iron replacement therapy: our study had a cross-sectional design. In addition, the ESR in our IDA subjects was higher than the ESR in TM patients. This might be because our IDA subjects had significantly lower Hb values than our TM patients; and, anemia is known to be one of the causes for a raised ESR.

Consequently, we diagnosed an increased frequency of FM in IDA and TM. FM was more frequent among IDA patients who were females, married, and had history of pica. Nonspecific symptoms in IDA and TM patients might not be explained by only anemia; and might not respond to therapy. In the presence of nonspecific symptoms, especially if there is CWP, FM should come to mind. In order to find out factors which affect the presence of FM in IDA and to determine response to iron replacement therapy, larger, longitudinal studies which assess anxiety–depression should be undertaken.

Conflict of interest statement None.

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