Frequency of juvenile fibromyalgia syndrome in children with familial Mediterranean fever: effects on depression and quality of life

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ABSTRACT

Objective. *To determine the prevalence of juvenile fibromyalgia syndrome (JFMS) in children with familial Mediterranean fever (FMF) and to evaluate quality of life (QoL) and depression.*

Methods. *Ninety-one FMF patients (M/F: 44/47) who fulfilled the Livneh criteria and 60 healthy children (M/F: 27/33) were enrolled in the study. Yunus and Masi's criteria were used for diagnosis of JFMS. Depression was assessed with Children's Depression Inventory (CDI) and QoL was evaluated with child and parent reports of Paediatric Quality of Life Inventory 4.0 (PedsQL™).*

Results. *While 20 (21.9%) of 91 FMF patients fulfilled JFMS criteria, 2 (3.3%) of the control group met the diagnostic criteria of JFMS (p=0.002). PedsQL™ scores (child self-report and parent-report) of the FMF patients were significantly lower and the depression scores were significantly higher than the healthy controls (p<0.001 for all). When the FMF patients were assigned to two groups as FMF with or without JFMS, patients with JFMS were found to have a higher depression score (p=0.007) and child and parent reports of PedsQL™ 4.0 were lower in the children with JFMS than in the patients without JFMS (p=0.001, p=0.003, respectively).*

Conclusion. *We have determined that JFMS frequency was higher in children with FMF and patients with FMF and JFMS had a poor QoL and were more susceptible to depression. FMF patients with widespread and persistent pain should be evaluated for JFMS in order to avoid unnecessary investigations and inappropriate treatment.*

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterised by recurrent self-limited episodes of fever and serosal inflammation accompanied by a marked acute-phase response. The disease is characterised mainly by fever with abdominal pain and/or arthritis (1). Most patients begin to suffer during childhood. Although the most common expression of musculoskeletal involvement in FMF is acute recurrent monoarthritis of short duration, muscle pain, chronic joint disease, spondylarthropathy, fibromyalgia, and myopathy are the additional rare manifestations (2).

Juvenile fibromyalgia syndrome (JFMS) is a chronic pain condition characterised by symptoms of diffuse musculoskeletal pain and multiple painful tender points. It is often accompanied by fatigue, poor sleep, chronic headaches, irritable bowel syndrome, and subjective soft tissue swelling (3, 4). Although the estimated overall prevalence of fibromyalgia syndrome (FMS) was 2.9% and 4.7% in the general population (5), patients with inflammatory diseases have a much higher frequency of FMS (13.4–55%) (6-8). Currently it is not clear whether the inflammatory disorder leads to FMS or vice versa, but possible mechanisms exist for both hypotheses. The coexistence of FMS and inflammatory disorders can lead to considerable difficulty in both diagnosis and treatment, and also concurrent FMS modifies the picture of the diseases (9). Although there are many studies investigating the prevalence of FMS in adults (6-8, 10-15), only one study has investigated the coexistence of JFMS and inflammatory disorders in children (16).

Various non-rheumatic chronic disorders and also rheumatic conditions were shown to have impact on health-related quality of life (HRQoL) in children (17, 18). The frequency of mood disorders,

such as depression and anxiety, is also higher in children and adolescents with chronic illness and rheumatic diseases and presence of these disorders may adversely affect QoL and the medical outcome of the patients (19, 20). Although impact of QoL and depressive disorders has been described in chronic conditions, much less is known about FMF. In the literature, there is only one study evaluating QoL in children with FMF (21) and one study investigating depression (22). The authors declared that FMF patients had lower HRQoL and were more depressed.

Many adolescent patients with JFMS have high levels of disability, difficulty attending regular school, difficulty with peer relationships, and increased emotional distress (23, 24). In addition, children with JFMS report more anxious and depressive symptoms than children with chronic inflammatory disorders or healthy controls. Children report that anxiety and stress play a significant role in the modulation of their pain (23-25). There is no published data simultaneously investigating prevalence of JFMS, HRQoL, and depression in children with FMF. The aims of the present study are to determine (i) the prevalence of JFMS in children with FMF, (ii) whether having FMF distorts the measures of QoL and depression, (iii) QoL and depression in patients with FMF and JFMS.

Materials and methods

Ninety-one FMF patients (M/F: 44/47) who fulfilled the Livneh criteria (26) and 60 healthy children (M/F: 27/33) were enrolled in the study. The FMF patients were evaluated in the outpatient clinic of Paediatric Nephrology. The criteria for recruitment were as follows: (1) between 8 and 18 years of age, (2) at least one year of diagnosis. Patients were excluded from the study if they had one of the following conditions: (1) presence of any other chronic or inflammatory disease that may cause JFMS other than FMF, (2) patients with amyloidosis. All of the patients and/or their legal guardian provided written informed consent, and the study was approved by the ethics committee of Ondokuz Mayis University.

Demographic data including age, body mass index (BMI), age at onset of the symptoms, duration of symptoms and family history were recorded. The patients were questioned about periodic fever, abdominal and chest pain, arthritis, and rash. None of the patients in the study had an acute attack at the time of evaluation. The severity score of the disease was calculated on the basis of the Tel-Hashomer Severity Score (27). Mediterranean fever (*MEFV*) mutations were determined in all patients. 46 of the patients were homozygous, 23 were compound heterozygous, and 22 were heterozygous for *MEFV* mutations. The most common *MEFV* mutation was M694V/M694V. The clinical characteristics of the patients are given in Table I.

All the patients and controls were evaluated in the Physical Medicine and Rehabilitation Department regarding the associated symptoms of JFMS, depression, and QoL. Yunus and Masi's criteria were used for diagnosis of JFMS (28). Yunus and Masi's criteria include the presence of diffuse musculoskeletal pain in at least three areas of the body that persists for at least 3 months. In addition to 5 or more typical tender points, the Yunus and Masi's criteria also require that 3 of 10 minor criteria or associated symptoms be present for diagnosis. These include fatigue, sleep disturbance, chronic anxiety or tension, chronic headaches, irritable bowel syndrome, subjective soft tissue swelling, numbness of tingling of the extremities, pain modulated by stress or anxiety, weather and physical activity.

Table I. Clinical characteristics of the FMF patients.

Clinical characteristics	
Age at onset of the symptoms (years)	6.93 ± 3.46
Duration of symptoms (years)	5.20 ± 3.27
Family history n (%)	51 (56%)
FMF symptoms n (%)	
Periodic fever	75 (82.4)
Abdominal pain	78 (85.7)
Chest pain	36 (39.6)
Arthritis (episodic)	42 (46.2)
Rash	12 (13.2)
Disease severity	7.19 ± 1.93

Measures

All subjects completed questionnaires assessing pain levels, depression, and functional disability. The following measures were used.

Pain

The global pain of the patients was assessed by visual analogue scale (VAS) pain score (0–10 cm, with higher scores indicating more pain).

Children's Depression Inventory

The Children's Depression Inventory (CDI) is a validated and widely used measure of depressive symptoms in children and adolescents and is frequently used to assess depressive symptoms in paediatric pain populations. Items on the CDI are categorised into 5 scales: negative mood, interpersonal problems, ineffectiveness, anhedonia, and negative self-esteem. For each item, adolescents choose 1 of 3 responses, representing varying symptom levels that best describe their symptoms for the past 2 weeks. Total score ranges from 0 to 54. Higher scores represent more severe depression. CDI scores of ≥19 are considered as clinically meaningful to identify significant depressive symptomatology (29, 30).

The PedsQL™ 4.0 (Paediatric Quality of Life Inventory™ Version 4.0)

The PedsQL™ 4.0 Generic Core Scales are comprised of parallel child self-report and parent proxy-report formats. The 23-item PedsQL™ 4.0 Generic Core Scales encompass: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items), and were developed through focus groups, cognitive interviews, pretesting, and field testing measurement development protocols. An accompanying parent completed the parent proxy-report of the PedsQL 4.0 (31, 32).

Statistical analysis

Statistical analyses were performed with SPSS 16.0 for Windows. Descriptive data were presented as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was used to analyse normal distribution of the quantitative outcomes.

Table II. Depression, child self-reported and parent proxy-reported PedsQLTM scores of pediatric patients with FMF and healthy children.

	Patients n=91	Controls n=60	*p*-value
CDI	10.54 ± 5.96	6.81 ± 5.66	0.001
Child self-report			
Physical functioning	510.71 ± 155.50	660.42 ± 123.44	0.001
Emotional functioning	339.12 ± 98.23	421.67 ± 81.62	0.001
Social functioning	417.58 ± 79.71	467.50 ± 49.20	0.001
School functioning	296.26 ± 89.19	406.67 ± 77.13	0.001
Total score	1563.68 ± 333.29	1956.25 ± 243.32	0.001
Parent proxy-report			
Physical functioning	451.10 ± 166.45	702.08 ± 101.08	0.001
Emotional functioning	303.02 ± 107.35	407.08 ± 83.87	0.001
Social functioning	398.35 ± 98.44	474.17 ± 42.17	0.001
School functioning	273.90 ± 91.96	403.75 ± 71.87	0.001
Total score	1426.37 ± 351.70	1987.08 ± 207.86	0.001

CDI: Children's Depression Inventory.

Table III. Clinical findings of the patients with and without JFMS.

	Patients with JFMS (n=20)	Patients without JFMS (n=71)	*p*-value
Age (years)	12.35 ± 3.51	12.18 ± 2.51	0.84
Sex (M/F)	6/14	38/33	0.06
BMI (kg/m^2)	19.20 ± 4.36	18.06 ± 3.51	0.22
Age at onset of the symptoms (years)	7.15 ± 4.70	6.87 ± 3.06	0.80
Duration of the symptoms (years)	5.15 ± 2.94	5.22 ± 3.38	0.90
Disease severity score	7.65 ± 2.27	7.01 ± 1.92	0.18
History of arthritis n (%)	12 (60%)	30 (42.3%)	0.16
Number of tender points	7.85 ± 2.60	2.28 ± 2.37	0.001
VAS	5.65 ± 1.98	4.40 ± 1.98	0.03
CDI	14.40 ± 7.42	9.46 ± 5.03	0.007
Child self-report			
Physical functioning	395 ± 141.09	543.31 ± 144.17	0.001
Emotional functioning	247.50 ± 97.63	364.93 ± 82.13	0.001
Social functioning	363.75 ± 107.75	432.75 ± 62.90	0.006
School functioning	259.25 ± 94.87	306.69 ± 85.35	0.03
Total score	1265.5 ± 353.68	1647.67 ± 276.24	0.001
Parent proxy-report			
Physical functioning	388.75 ± 128.11	468.66 ± 172.46	0.05
Emotional functioning	233.75 ± 91.14	322.54 ± 103.95	0.001
Social functioning	361.25 ± 99.82	408.80 ± 96.18	0.04
School functioning	236.25 ± 99.49	284.51 ± 87.56	0.03
Total score	1220 ± 358.50	1484.50 ± 329.48	0.003

CDI: Children's Depression Inventory; VAS: Visual Analogue Scale.

To compare two groups Mann-Whitney U-test and *t*-test were used when needed according to the normal distribution of the parameters. The association between the groups was analysed using chi-square and Fisher exact tests when feasible. The relation between variables was assessed by Pearson and Spearman's tests, where appropriate. *P*-values less than 0.05 were considered statistically significant.

Results

The mean ages of the FMF patients and control group were 12.21±2.74 years and 12.23±2.47 years, respectively. The BMI was 18.31±3.71 for the patients and 19.26±3.34 for the control subjects. There were no significant differences between FMF patients and the control group in terms of age, gender or BMI ($p>0.05$).

The parent proxy-report and child self-reported PedsQL™ scores of children with FMF were significantly lower than healthy peers ($p<0.001$, $p<0.001$, respectively). The depression scores of patients with FMF were also significantly higher than the healthy controls ($p<0.001$) (Table II).

While 20 (21.9 %) of 91 children with FMF fulfilled the criteria for the diagnosis of JFMS**,** 2 (3.3 %) of the control group met the diagnostic criteria of JFMS ($p=0.002$)**.** The frequency of JFMS was 13.6% (6 boys) among boys and 29.8% (14 girls) among girls. Although frequency was higher in the girls, this difference did not reach a significant difference ($p=0.06$).

The FMF patients were assigned to two groups as FMF with JFMS or FMF without JFMS. There was no statistically significant difference between the groups regarding the age, BMI, age at onset of the symptoms, duration of the symptoms and disease severity score ($p>0.05$). While 20 (100%) of the patients with JFMS had widespread pain, 3 (4.2) of the patients without JFMS had widespread pain ($p=0.001$). Fatigue (100%), sleep disturbance 75(%), chronic headaches (60%), and pain modulated by physical activity (60%) were the most common associated symptoms in the patients with JFMS. Fatigue, sleep disturbance, chronic anxiety or tension, numbness of tingling of the extremities and pain modulated by weather were more frequent in the patients with FMF and JFMS ($p<0.05$).

The demographic and clinical characteristics of patients with and without JFMS are shown in Table III. The number of tender points and VAS pain score were higher in the patients with JFMS ($p<0.05$). Patients with JFMS had a higher depression score ($p=0.007$) and 6 (30%) of FMF patients with JFMS and 2 (2.8%) of patients without JFMS had depression according to the cut-off value of ≥19 ($p<0.001$). Total scores of PedsQL™ 4.0 (child self-report and proxy-report) were also lower in the children with JFMS than in the patients without JFMS ($p=0.001$, $p=0.003$, respectively). There were no correlations between the disease severity score and total scores of PedsQL™ 4.0 (child self-report and proxy-report) and depression score in the patients with JFMS ($p>0.05$).

Discussion

To our knowledge this is the first study assessing JFMS frequency along with the HRQoL, and depression in children with FMF. The JFMS prevalence of 21.9% among our FMF patients was significantly higher than that of among the healthy controls.

In adults, FMS frequency was estimated to be between 2.9 to 4.7% of the general population (5), whereas it is reported to be ranging from 1.2% to 6.2 in children (33-35). Recently, a study reported by Durmaz *et al*. (36) revealed that 5.5% of Turkish children had JFMS. It is estimated that prevalence is also higher in paediatric rheumatology clinics and JFMS represents 7–40% of new referrals (23, 24). JFMS may exist as primary or secondary, on the basis of the presence or absence of a variety of chronic disorders and rheumatic diseases. Previous reports indicated the higher frequency of FMS in individuals with inflammatory rheumatic disorders than expected. FMS is a well-known secondary feature of many rheumatic diseases such as rheumatoid arthritis (13.4–17.1%) (6, 10), systemic lupus erythematosus (22.1–35.7%) (14,15), Sjögren's syndrome (20–55%) (8,12), Behçet's disease (9.2–37.1%) (7,13), and AS (4.11%) (11). Langevitz (37) and Cengiz (38) have demonstrated that 32% and 23.4% of adult patients with FMF had concurrent FMS. Although there are many studies investigating the coexistence of FMS and rheumatic diseases in adult population, only one study in the literature examined the relationship of two diseases in children. In their study, Kasapcapur *et al*. (16) detected JFMS in 2 (1.8%) of 108 FMF patients with no significant difference in the prevalence of JFMS between patients with FMF and healthy children. Discrepancy between the two studies may be due to the differences in sample type and used diagnostic criteria. The ACR criteria used in the Kasapcapur's study require more tender points and do not include the presence of associated symptoms.

Since the prevalence of JFMS is high in school-aged children and the treatment is completely different, it is important to distinguish JFMS from other rheumatic diseases in the clinical setting. The development of JFMS may go unrecognised, especially when it develops after a rheumatologic disease. Additionally, an individual with JFMS alone might be misdiagnosed as having an inflammatory disorder leading to inappropriate treatment. Many investigators have hypothesised that autoimmune diseases occur first and then lead to FMS. Conversely, it is conceivable that FMS actually precedes and predisposes the individual to an autoimmune disorder. A number of potential mechanisms have been proposed to explain the relationship between FMS and inflammatory diseases. A pre-existing hypoactive stress response might lead to an inflammatory disorder. Alternatively, the inflammatory disorder may occur first, and the sustained activation of the stress response by immune mediators might lead to subside of the capabilities of this system. Another potential mechanism is pain and disturbed sleep caused by an inflammatory disorder which might lead to FMS (9).

Chronic health conditions have significant impact on both children and their families in terms of pain, emotional, developmental and behavioural disorders. HRQoL is an important outcome measure in understanding the impact of chronic illness, including childhood-onset rheumatic diseases, and has been increasingly recognised as an important domain to be included in therapeutic trials of patients with chronic rheumatic diseases (39, 40). Previously, impact of chronic disorders and also rheumatic diseases on QoL was evaluated in several studies in adults and also in children (17, 18). However, there are very limited data on children with FMF (21). In the present study, children with FMF had a higher depression score and the parent proxy-report and child self-reported PedsQL™ scores of the patients were significantly lower than the healthy controls. Two recent studies conducted in adults revealed that HRQoL was significantly impaired in FMF patients and depression is more frequent in FMF patients than in healthy subjects (38, 41). There is only one study investigating QoL in children with FMF. Makay *et al*. (21) evaluated the parent proxy-reported and child self-reported HRQoL of school-age children with FMF and showed that HRQoL of children with FMF was impaired when compared with healthy peers. Children with an inflammatory disorder commonly experience acute and chronic pain, decreased mobility, growth retardation, frequent visits to the doctor, restrictions on activities and school absenteeism. Increasing physical disability in children with an inflammatory disorder is also associated to an increased incidence of depression, and presence of this disorder may adversely affect QoL, medical outcome and duration of treatment (40, 42). Recently, Makay *et al*. (22) suggested that patients with FMF were considerably more depressed than their healthy peers.

Since JFMS causes subjective distress and a few objective abnormalities on standard physical examination and laboratory screening is detected, it is an exceptionally wearisome experience for patients and health care providers. Approximately 25% to 40% of children with pain syndromes can be diagnosed with JFMS. Children and adolescents with JFMS and musculoskeletal pain have been shown to have high levels of disability, significant psychosocial distress including depression, behaviour problems, anxiety, social difficulties, and withdrawal from school and social activities (23-25, 30). In our study we also evaluated the coexistence of FMF and JFMS regarding the clinical findings, QoL and depression. In the literature, nonrestorative sleep (100%), fatigue (91%), chronic anxiety or tension (56%), chronic headaches (54%), and subjective soft tissue swelling (61%) are reported as the most common associated symptoms of the JFMS (28). Consistent with the literature, fatigue (100%), non-restorative sleep (75%), chronic headaches (60%) and widespread musculoskeletal pain are the most common findings of the FMF patients with JFMS. Along with pain, fatigue and sleep disturbance are critical contributors to the impact of chronic illness on multiple domains of functioning (43). We found that widespread pain, fatigue and also VAS pain score were higher in the patients with JFMS.

In the present study, HRQoL, in all four subscales scores, is significantly impaired in FMF patients with JFMS. These patients also have increased risk of depression which might facilitate the impairment of QoL and mental health. Although JFMS and other rheumatologic childhood diseases differ regarding pathogenesis and treatment response, they can present similar clinical findings such as fatigue and pain. Therefore, distinguishing JFMS from other rheumatologic diseases is important in terms of avoidining unnecessary investigations and planning the early treatment.

We did not demonstrate a significant difference between patients with and without JFMS regarding the disease severity in the present study. Moreover, there was no correlation between the disease severity and QoL, and depression. These results suggest that impairment of QoL and development of depression is free of disease severity in patients with JFMS. Therefore all FMF patients with diffuse pain, regardless of the disease severity, should be evaluated for the concurrent JFMS.

In conclusion, we have determined that JFMS frequency was higher in children with FMF than in the normal population. Impairment in QoL and depression were more common in FMF patients than in healthy children. Also patients with FMF and JFMS had a poor QoL and were more susceptible to depression regardless of disease severity. We conclude that FMF patients with widespread and persistent pain should be evaluated for JFMS in order to avoid unnecessary investigations and inappropriate treatment.

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