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Evaluation of Restless Legs syndrome and growing pains in children with familial Mediterranean fever

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SUMMARY: Altuğ-Gücenmez Ö, Makay B, Kaçar A, Ünsal E. Evaluation of restless legs syndrome and growing pains in children with familial Mediterranean fever. Turk J Pediatr 2018; 60: 159-164.

Growing pains (GP) and restless leg syndrome (RLS) are one of the frequently seen pain syndromes of childhood. These two pain syndromes -GP and RLS- may be confused with exertional leg pain (ELP) of familial Mediterranean fever (FMF). The aim of this study was to evaluate the frequency of fulfilling the criterion for GP and RLS among children with FMF. Sixty FMF patients and 70 healthy controls were enrolled. Clinical and demographic data of patients were recorded. A questionnaire including the symptoms of GP and RLS were applied to all participants and their parents. Twenty-seven patients (45%) had ELP. Ten FMF patients and 10 healthy children fulfilled GP criteria. There was not a significant difference between patients and controls regarding GP. Three FMF patients and 7 healthy controls fulfilled RLS criteria. There was not a significant difference between two groups regarding RLS. Two out of 27 FMF patients with ELP had RLS while one out of 33 FMF patients without ELP had RLS. Eight out of 27 FMF patients with ELP fulfilled GP criteria while two out of 33 FMF patients without ELP fulfilled GP criteria (p=0.01). There was a significant inverse correlation with FMF severity score and GP (p=0.003 and r=-0.376). There was not a significant association with FMF severity score and RLS. This study suggested that GP and RLS are not more common in pediatric FMF patients than their healthy peers.

Key words: Exertional leg pain, familial Mediterranean fever, growing pains, restless legs syndrome.

Familial Mediterranean fever (FMF) is an autosomal recessively-inherited auto-inflammatory disease characterized by recurrent attacks of fever and serositis, such as peritonitis, pleuritis and arthritis and it is most commonly seen in Sephardic Jews, Turks, Arabs, and Armenians.[1,2] The disease-causing gene MEFV (Mediterranean FeVer) encodes a protein called pyrin or marenostrin, which regulates interleukin-1 β production.[1,2] Musculoskeletal complaints such as arthritis, arthralgia, and myalgia are frequently seen among patients with FMF.[1-4] A substantial number of patients complain about bilateral leg pain induced by exercise, which is regarded among the minor diagnostic criteria of the disease.[5] Exertional leg pain (ELP) is a musculoskeletal manifestation in FMF, occurring in up to 29-58.2-% of patients.[3,4,6] These patients have myalgia and arthralgia lasting for a few hours to whole day, mainly affecting the legs following a physical exertion or even prolonged standing.

Growing pains (GP) are one of the frequently seen pain syndromes of the childhood period. Growing pains are the bilateral and intermittent leg pain, which are seen in young children generally in the evening and at night.[7] Restless legs syndrome (RLS) is a disorder characterized by an irritating feeling on the legs and the uncontrolled stimulation of moving the legs while resting in order to remove this feeling.[8,9] These two pain syndromes -GP and RLS- may be confused with ELP of FMF. To our knowledge there has been no studies evaluating "restless legs syndrome" and "growing pains" in FMF patients. The aim of this study is to evaluate

the frequency of fulfilling the criterion for GP and RLS among children with FMF.

Material and Methods

Study population

Patients diagnosed with FMF according to the pediatric FMF criteria[10] followed at the Department of Pediatrics, Division of Rheumatology in a tertiary hospital, were consecutively enrolled in the study. FMF patients who had concomitant chronic diseases such as juvenile idiopathic arthritis were not included. Healthy children who were matched for age and sex constituted the control group. This cross-sectional study was conducted between November 2014 and May 2015. All of the patients were on colchicine treatment for at least 6 months. None of the patients in the study were in an acute attack period at the time of evaluation. The attack-free period was defined as 'at least 2 weeks after an attack'.

Methods

Demographic data, FMF symptoms, MEFV mutation, age at disease onset, disease duration, duration of follow-up, disease severity scores, and dose of colchicine were recorded for each patient. The disease severity score was calculated according to the scoring system suggested by Pras et al.[11]. Additionally; serum ferritin, iron and iron binding capacity were measured in order to evaluate iron deficiency anemia. A questionnaire including the symptoms of GP and RLS were applied to all participants and their parents. The study protocol was approved by the ethics committee of Dokuz Eylül University, Faculty of Medicine. Parents and children were informed about the questionaire and the procedure. All participants gave their informed consent prior to their inclusion in the study.

Assessment of GP

Growing pains were diagnosed by clinical interview and physical examination. The determination of GP was based on the definition outlined by Peterson[12] and applied in published studies, e.g., Champion et al.[13]. In this study, four major inclusion criteria and three exclusion criteria were used to define GP (Table I). Four additional features were included to assist in classification of ambiguous cases.[13]

Assessment of RLS

Restless legs syndrome was diagnosed according to the essential criteria of the National Institutes of Health RLS diagnostic criteria for children and adults, as presented in Table II.[8,9] These criteria apply to both adults and children, but it is required that children are able to describe the leg sensations in their own words to meet the criteria for definite RLS.

Table I. Criteria for Growing Pains.

Essential growing pain criteria[a]
1. Pain in both legs
2. Pain started between 3 and 12 years
3. Pain typically occured at the end of the day or during the night
4. No significant limitation of activity and no limping
Excluding factors
1. A pattern of pain severity not consistent with a diagnosis of growing pains
2. Any indication of a definite orthopedic disorder
3. Any abnormalities on spesific testing (e.g., X-rays, bone scans)
Additional descriptive features of growing pains[b]
1. Pain persisted at least 3 months
2. There were periods of days, weeks, or months without leg pains
3. Pain was not a problem in the morning
4. There was no associated lack of well-being

[a] If at least three of four essential growing pains characteristics were present, in the absence of any excluding factors, the individual was classified as fulfilling criteria for growing pains.
[b] Additional features for determining ambiguous cases.

Statistical analysis

Data was evaluated using the Statistical Package for Social Sciences 11.0 program for Windows (SPSS Inc., Chicago, IL, USA) and by analyzing descriptive statistics (means, standard deviation) and by comparing dual groups using Student's t-test and Mann–Whitney U-test when appropriate. Chi-square test was used to evaluate the differences in proportions. P-values ≤0.05 were considered as significant. Intercorrelations between parameters were computed through Pearson's correlation analysis. Correlation coefficients indicated low correlation at 0.10–0.29, medium correlation at 0.30–0.49, and high correlation at ≥0.50.

Results

A total of 60 patients (29 females and 31 males) with FMF and 70 healthy controls (36 females and 34 males) were enrolled in the study. Mean age of the FMF patients was 9±3.8 years, and controls were 9.8±3.7 years. No significant difference considering age and gender was found between the patients and the controls. The clinical characteristics of the patients were given in Table III. Mediterranean fever (MEFV) mutations were identified in all patients. Twelve patients (19%) were homozygous for M694V mutation, and 20 other genotypes were present in the remaining 48 patients. Thirty-one patients (52%) had a family history for FMF.

Twenty-seven patients (45%) had ELP. Ten FMF patients and 10 healthy children fulfilled GP criteria. There was not a significant difference between patients and controls regarding GP (p=0.44). Three FMF patients and 7 healthy controls fulfilled RLS criteria. There was not a significant difference between two groups regarding RLS (p=0.23). Two out of 27 FMF patients with ELP had RLS while one out of 33 FMF patients without ELP had RLS (p=0.439). Eight out of 27 FMF patients with ELP fulfilled GP criteria while two out of 33 FMF patients without ELP fulfilled GP criteria (p=0.01). No significant difference was found, when the patients with ELP who fulfilled and did not fulfill GP criteria were compared regarding clinical symptoms of FMF, such as fever, peritonitis, pleuritis, and arthritis. These both groups were also similar regarding current age and age at symptom onset (p=0.65 and p=0.69, respectively).

Nine patients had anemia according to their ages, which was not consistent with iron deficiency anemia. They had anemia of chronic disease according to laboratory parameters. There was not a significant association with

Table II. Criteria for RLS in Adults and Children.

Essential diagnostic criteria for RLS in adults:

1. An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs).
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).

Criteria for the diagnosis of definite RLS in children:

1. The child meets all 4 essential adult criteria for RLS and
2. The child relates a description in his/her own words that is consistent with leg discomfort (the child may use terms such as 'owies, tickle, spiders, boo-boos', 'want to run' and 'a lot of energy in my legs' to describe symptoms. Age-appropriate descriptors are encouraged.

Table III. Demographics of FMF Patients.

Variable	
Disease duration (years)	
Range	0.5-12
Mean±SD	3.5±2.5
Age at disease onset (years)	
Range	0.5-15
Mean±SD	4.3±3.5
Dose of colchicine (mg/day)	
Range	0.5-2
Mean±SD	1±0.4
Severity score (%)	
1	23 %
2	70 %
3	7 %
FMF symptoms (%)	
Fever	84.6 %
Peritonitis	83.3 %
Pleuritis	21.7 %
Arthritis (episodic)	51.7 %
Rash	3.3 %
ELP	45 %
Nephropathy/Amyloidosis	0 %
MEFV mutation (%)	
M694V homozygous	19 %
Others	81 %

anemia and GP, and as well as RLS (p=0.62 and p=0.36, respectively). There was a significant inverse correlation with FMF severity score and GP (p=0.003 and r=-0.376). Besides, there was not a significant association with FMF severity score and RLS (p=0.626 and r=-0.043).

Among all participants, only one child who fulfilled RLS criteria also fulfilled GP criteria. There was not a significant association between gender and GP, and as well as RLS (p=0.33 and p=0.19, respectively)."

M694V homozygous patients had similar GP and RLS rates when compared to patients with other mutations (p=0.9, and p=0.37, respectively).

Discussion

The results of this study indicated that patients with FMF had similar rates of GP and RLS when compared to their healthy peers. Additionally, patients with ELP more commonly fulfilled GP criteria than the patients without ELP with a statistical significance. However, there was not an association between ELP and RLS. To the best of our knowledge, this is the first study investigating the frequency of fulfilling the criterion for GP and RLS among children with FMF. Therefore, there is no other study available as such to be compared with our results.

Exertional leg pain, occurring after mild exercise or physical activity, is a characteristic musculoskeletal manifestation of FMF. The 45 percent of FMF patients had exertional leg pain in this study, the frequency of ELP in our study is in agreement with those in previous literature.[4,14] In a nationwide multi-center study of the Turkish FMF Study Group, the prevalence of ELP was reported as 39.6%.[14] Eshed et al.[3], reported a higher rate of ELP among Israelian FMF patients. The prevalence of ELP among the 170 FMF patients included in that study was 58.2%. In the study of Majeed et al.[4], 25 % of patients from Jordan had myalgia of whom 81% of them was in an exercise-induced pattern.

Growing pain is a non-inflammatory pain syndrome, particularly affecting children between 3-12 years of age.[7,12] The child complains of lower limb pain appearing in the evening or at night often awaking the child, which is almost always pain free by the morning. The pathogenesis of GP is not

exactly known. The rate of fulling GP criteria among FMF patients with ELP was higher than the patients without. Eight of 27 FMF patients with ELP and 2 of 33 FMF patients without ELP fulfilled GP criteria (p=0.01). This result considered that clinicians must have a "high index of suspicion" for FMF when evaluating a child suspected to have GP in certain ethnic groups. Growing pains may be confused with ELP of FMF. A detailed history for the other clinical manifestations of FMF must be investigated.

Although the exact pathogenesis is unknown, RLS is accepted as a neurological, sensorimotor disorder affecting sleep.[7] We previously showed that children with FMF had more sleep disturbances than their healthy peers and exertional leg pain was associated with poor sleep quality.[15] Restless legs syndrome may be seen secondary to some diseases, particularly iron deficiency anemia.[16,17] Many diseases such as rheumatoid arthritis, Parkinson disease, multiple sclerosis, and chronic renal insufficiency were shown to be associated with RLS.[18] The results of this study showed that FMF is not a disease related to RLS. Previous literature also indicated a significant association between GP and RLS.[7,13] However, only one child who fulfilled RLS criteria also fulfilled GP criteria in this study. Our results failed to show an association between GP and RLS.

The limitations of this study include the small sample size and the inclusion of children who were all attending the same rheumatology clinic, which may limit the geographic, racial and ethnic diversity of the sample. As a result, it is necessary to be cautious when generalizing the results of this study to all children with FMF.

In conclusion, the results of this study suggested that GP and RLS are not more common in pediatric FMF patients than their healthy peers. However, due to the limited number patients, further researches are needed to confirm our results.

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