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ARAŞTIRMA / RESEARCH

Frequency of functional gastrointestinal disorders in children with juvenile idiopathic arthritis

Juvenil idiyopatik artritli çocuklarda fonksiyonel gastrointestinal hastalıkların sıklığı

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Abstract

Purpose: The aim of this study was to compare the frequency of functional gastrointestinal diseases (FGIDs) in juvenile idiopathic arthritis (JIA) patients with healthy control children.

Materials and Methods: This case-control study includes 193 children with JIA followed-up between October 2012 to April 2019 and 139 healthy control children. Demographic features, disease characteristics, treatment modalities were collected retrospectively. Laboratory parameters were recorded at the study enrollment. FGIDs diagnosis were assessed by utilizing Rome IV criteria. Gender, age at disease onset, laboratory parameters, treatment modalities, and clinical status of the disease were compared between the groups.

Results: The mean age at study enrollment was 12.05±4.05 and 9.01±3.97 years in children with JIA and healthy control group, respectively. The frequency of FGIDs was significantly higher in JIA patients (13.7%, n=19) than in healthy control group (21.8%, n=42). There was no statistical significance between JIA patients and healthy control group in terms of FGIDs subtypes. Demographic and clinical parameters did not differ between JIA patients grouped according to FGIDs presence.

Conclusion: FGIDs is more frequent in JIA patients than healthy controls. Further studies are needed to support our results.

Keywords: Juvenile idiopathic arthritis, functional gastrointestinal disorders, Irritable bowel syndrome.

Öz

Amaç: Bu çalışmada juvenil idiyopatik artriti (JIA) olan çocuklarda fonksiyonel gastrointestinal hastalıklar (FGH) görülme sıklığının sağlıklı çocuklarla karşılaştırması amaçlanmıştır.

Gereç ve Yöntem: Bu vaka-kontrol çalışması Ekim 2012 ve Nisan 2019 tarihleri arasında izlemde olan JIA tanılı 193 çocuk ve 139 sağlıklı kontrol çocuk içermektedir. Demografik özellikler, hastalık karakteristikleri, tedavi yaklaşımları geriye dönük olarak toplandı. Çalışma yürütüldüğü esnada laboratuvar parametreleri kaydedildi. FGH tanısı Roma IV kriterlerine göre değerlendirildi.. Cinsiyet, hastalık başlangıç yaşı, laboratuvar parametreleri, tedavi yaklaşımları ve hastalığın klinik durumu iki grup arasında karşılaştırıldı.

Bulgular: Çalışma esnasında ortalama yaş JIA hastalarında 12,05±4,05 yıl ve kontrol grubunda 9,01±3,97 yıl idi. FGH hastalık sıklığı JIA hastalarında (%21,8 n=42) kontrol grubuna göre (%13,7, n=19) anlamlı düzeyde yüksekti. FGH subtipleri açısından JIA hastaları ve kontrol grup arasında istatistiksel anlamlılık yoktu. Demografik ve klinik parametreler FGH varlığına göre gruplandırılan JIA hastaları arasında farklı değildi.

Sonuç: JIA hastalarında kontrol grubuna göre FGH daha sık görülmektedir. Sonuçlarımızın destekleyici daha fazla çalışmaya ihtiyaç duyulmaktadır.

Anahtar kelimeler: Juvenil idiyopatik artrit, fonksiyonel gastrointestinal hastalıklar, irritabl barsak sendromu.

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood[1,2]. JIA is classified into several subgroups in line with International League of Associations for Rheumatology (ILAR) classification criteria, that all manifesting joint inflammation but present with various clinical characteristics[3]. The proinflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor-necrosis factor-α (TNF-α) play an important role in JIA pathogenesis in which these cytokines lead to chronic inflammation by local and systemic effects[4]. Disease modifying anti-rheumatic drugs (DMARDs) are the mainstay modalities in JIA treatment. For the past decades, the treatment of JIA has been greatly improved with introducing biologic agents which controls the disease activity much better, thus improving the quality of life of the patients[5,6].

Functional gastrointestinal disorders (FGIDs) are heterogenous diseases with unclear pathophysiology and characterized by chronic or recurrent abdominal pain or change in bowel habits such as defecation alterations[7,8]. Traditionally FGIDs were defined by the absence of structural or biochemical abnormalities. However, increased awareness of FGIDs lead to substantial progress in regard to its pathophysiology. Recent advances revealed that disruptions in the intestinal microbiota, low-grade inflammation of mucosa, immune activation, changed intestinal permeability are the underlying pathophysiology of FGIDs[9,10].

Recently, increased frequency of FGIDs in children and adults have been reported in several inflammatory diseases, including familial Mediterranean fever (FMF), Henoch-Schönlein purpura (HSP), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA)[11-15]. Since there is a growing evidence on underlying inflammatory processes of FGIDs and JIA is the leading inflammatory disease in childhood, we aimed to investigate the possible association between FGIDs and JIA. Therefore, we conducted this study to evaluate the FGIDs frequency and susceptibility factors in children with JIA compare to the healthy control group.

MATERIALS AND METHODS

The current study includes 193 JIA patients and 139 healthy children from Turkish descent. JIA patients were diagnosed between October 2012 to April 2019 according to ILAR classification criteria in the department of pediatric rheumatology, followed-up at least six consecutive months from disease onset were included to the study. Participants having red flag signs for organic gastrointestinal diseases, including serious vomiting, chronic diarrhea, weight loss, bloody stool, and having inflammatory bowel disease in their family were excluded[16].

The control group consisted of healthy children aged between 4 and 18 years, without chronic diseases, and abovementioned signs of organic gastrointestinal diseases. Informed consent was given by the parents of each patient before study enrollment. Approval of Ethics Committee of Cukurova University Medical Faculty (Number: 86/22, Date: 8 March 2019) was taken.

Procedure

JIA patients were sub-grouped according to ILAR classification criteria as follows: oligoarticular JIA, rheumatoid factor (RF) positive polyarticular JIA, RF-negative polyarticular JIA, systemic-onset JIA (soJIA), enthesitis-related arthritis (ERA)[3]. Demographic features including, gender, age at both symptom onset and diagnosis, disease subgroups, treatment modalities, the clinical status of the disease were retrospectively collected from medical files. Laboratory parameters, including whole blood count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) studied at last visit before assessment of FGID were also recorded. According to Wallace criteria, the clinical status of JIA patients was described as inactive disease, clinical remission on medication, clinical remission off medication[17].

Diagnosis of functional gastrointestinal disorders

Rome IV criteria was utilized to diagnose FGIDs at study enrollment, in patients with JIA and in healthy children, in which FGIDs classified in three parts as follows: functional nausea and vomiting disorders, functional abdominal pain disorders (FAPD) and functional defecation disorders[16]. Cyclic vomiting syndrome, functional vomiting, rumination syndrome, aerophagia, abdominal migraine, and non-retentive fecal incontinence were not observed in either JIA patients or healthy control group.

Diagnostic criteria for functional nausea must include

the following criteria for the last two months: predominantly annoying nausea unrelated to meals, not always associated with vomiting and occurring at least twice a week.

Functional dyspepsia was diagnosed if patients suffered from one or more of the following criteria at least four days per month for the last two months: postprandial fullness, early satiation, epigastric pain or burning unrelated to defecation. Irritable bowel syndrome (IBS) diagnosis requires the occurrence of abdominal pain at least four days per month and related to at least one of the following criteria for the last two months: related to defecation, changes in frequency of stool, and changes in appearance of stool plus persistence of symptoms even after resolution of the constipation. Functional abdominal pain was diagnosed with the presence of episodic or abdominal pain at least four times per month in the last two months in patients not meeting criteria of functional dyspepsia and IBS. Moreover, functional constipation was defined when patients had at least two of the following criteria, at least once a week for at last one month and insufficient criteria for a diagnosis of IBS: two or less defecations for a week, at least one episode of fecal incontinence in a week, retentive posturing or volitional stool retention, painful bowel movements, presence of a large fecal mass in rectum and presence of large diameter stool. For the diagnosis of all types of FGIDs, it is necessary that all patients undergo appropriate evaluation for another medical condition that could fully explain the symptoms[7].

Statistical analysis

SPSS 20.0 statistical software package (IBM SPSS Statistics) was used to perform the statistical analyses. Categorical variables were presented as numbers and percentages. Continuous variables were expressed as mean and standard deviation, as median and minimum–maximum according to their distribution. Gender and subsets of functional gastrointestinal disorders' frequencies were compared between JIA patients and healthy control group by Chi-square test. Mean age at study-onset was compared between these groups by performing Student T-test. Age at diagnosis, age at study enrollment and laboratory parameters including WBC, hematocrit, platelet count were compared between JIA patients with and without FGIDs by Student T-test, whereas diagnostic delay, disease duration and laboratory parameters including ESR and CRP were compared between these two groups by Mann–Whitney U test due to the distribution results according to the Kolmogorov-Smirnov test. Frequencies of treatment agents, active/inactive disease, remission and relapse rates were compared between JIA patients by utilization of Chi-square test. A *P* value less than 0.05 was regarded as statistically significant.

RESULTS

Totally, 193 JIA patients (110 females, 83 males) and 139 (52 females, 87 males) healthy children as a control group were included to the current study. While median age at diagnosis of JIA was 7.46 (range, 0.5 3-17.20) years, median diagnostic delay was 3.02 (range, 0.82-69.55) months and median disease duration was 3.22 (range, 0.51-16.96) years. Demographic features of JIA patients were given in Table 1 in detail.

The most frequent JIA subgroup was oligoarticular type in 71 (38.8%) patients followed by soJIA (n=42, 21.8%) subtype. All JIA patients were treated with non-steroidal anti-inflammatory drugs (NSAIDs). Corticosteroid was prescribed in 29% of patients (n=56) and at least one biologic agent was administered in 62.7% (n=121) of patients. Clinical characteristics of JIA patients were given in Table 1 in detail.

The frequency of presence of at least one FGID was 21.8% (n=42) among JIA patients and 13.7% (n=19) in control group, between which the difference was significant (p=0.04). Although FGIDs frequency was statistically significant in JIA patients compared with healthy control group, there was no statistical significance between the groups in terms of FGIDs subtypes. Overall, comparison of FGIDs frequency and its subgroups in JIA patients and in healthy control group were given in Table 2.

Furthermore, JIA patients were grouped according to presence and absence of FGIDs to determine the susceptibility factors related to FGIDs in JIA patients. Disease characteristics, laboratory parameters, treatment modalities, clinical status of the disease were compared between the groups. There was no statistical significance between the groups in terms of aforementioned parameters which were given in Table 3.

Table 1. Demographic features and clinical characteristics of 193 juvenile idiopathic arthritis patients.

Parameters		**N (%)**
Demographic features	Female/Male, n (%)	110 (57)/83 (43)
	Age at diagnosis, years, mean±SD*	7.81±4.40
	Diagnostic delay, months, median (range)	3.02 (0.82-69.55)
	Age at study time, mean±SD	12.05±4.05
	Disease duration, years, median (range)	3.22 (0.51-16.96)
JIA subgroups	Oligoarticular, *n (%)*	71 (36.8)
	Systemic onset, *n (%)*	42 (21.8)
	Enthesitis-related arthritis, *n (%)*	39 (20.2)
	RF-negative, *n (%)*	27 (14)
	RF-positive, *n (%)*	7 (3.6)
	Juvenile psoriatic arthritis, *n (%)*	4 (2.1)
	Undifferentiated, *n (%)*	3 (1.6)
Treatments	NSAIDs, *n (%)*	193 (100%)
	Corticosteroid, *n (%)*	56 (29)
	DMARDs, *n (%)*	187 (96.9)
	Biologic agents, *n (%)*	121 (62.7)
Acute phase reactants at study time	WBC; mm3, mean±SD	7960±2110
	Hematocrit; %, mean±SD	37.5±3.1
	Platelet count; mm3, mean±SD	328000±88570
	ESR; mm/h, median (range)	9 (2-85)
	CRP; mg/dl, median (range)	0.2 (0.1-8)
Clinical status	Active disease, *n (%)*	21 (10.9)
	Inactive disease, *n (%)*	25 (13.0)
	Clinical remission on medication, *n (%)*	121 (62.7)
	Clinical remission off medication, *n (%)*	26 (13.5)
	Relapses, *n (%)*	57 (29.5)

*SD; Standard deviation, RF; Rheumatoid factor, NSAIDs; Non-steroidal anti-inflammatory drugs, DMARDs; Disease modifying anti-rheumatic drugs, WBC; White blood count, ESR; Erythrocyte sedimentation rate, CRP; C-reactive protein.

Table 2. The comparison of demographic features and frequency of functional gastrointestinal disorders in patients with juvenile idiopathic arthritis and in healthy control group.

Parameters	**JIA patients (n=193)**	**Healthy control group (n=139)**	**p**
Age at study time, mean±SD	12.05±4.05	9.01±3.97	0.509
Female/Male, *n (%)*	110 (57)/83 (43)	67 (48.2)/72 (51.8)	0.070
FGIDs, *n (%)*	42 (21.8)	19 (13.7)	**0.040**
Multiple FGIDs, *n (%)*	11 (5.7)	6 (4.3)	0.383
Functional nausea, *n (%)*	5 (2.6)	1 (0.7)	0.407
Functional dyspepsia, *n (%)*	16 (8.3)	11 (7.9)	0.535
Irritable bowel syndrome, *n (%)*	7 (3.6)	3 (2.2)	0.334
Diarrhea predominant, *n (%)*	4 (2.1)	2 (1.4)	0.505
Constipation predominant, *n (%)*	3 (1.6)	1 (0.7)	0.443
Functional abdominal pain, *n (%)*	8 (4.1)	4 (2.9)	0.384
Functional constipation, *n (%)*	10 (5.2)	4 (2.9)	0.228

JIA; Juvenile idiopathic arthritis, SD; Standard deviation, FGIDs; Functional gastrointestinal disorders., Paired t-test was utilized for comparison of data. Significant p values ($p<0.05$) are presented in bold.

Table 3. Demographic features and disease characteristics of patients with juvenile idiopathic arthritis according to the presence and absence of functional gastrointestinal disorders

Parameters	JIA patients with FGIDs n=36	JIA patients without FGIDs n=157	p
Female/Male, n (%)	19 (52.8)/17 (47.2)	91 (58)/66 (42)	0.350
Age at diagnosis, years, mean±SD	7.81±4.40	7.78±4.58	0.967
Diagnostic delay, months, median (range)	2.98 (0.99-69.55)	3.15 (0.82-59.99)	0.656
Age at study enrollment, mean±SD	11.74±3.85	12.12±4.10	0.605
Disease duration, years, median (range)	3.18 (0.51-14.07)	3.22 (0.52-16.96)	0.534
Corticosteroid, n (%)	8 (22.2)	48 (30.6)	0.416
DMARDs, n (%)	36 (100)	151 (96.2)	0.596
Biologic agents, n (%)	21 (58.3)	100 (63.7)	0.570
WBC; mm3, mean±SD	7640±1822	8034±2170	0.314
Hematocrit; %, mean±SD	37.3±2.7	37.5±3.2	0.738
Platelet count; mm3, mean±SD	335000±74817	326000±91573	0.593
ESR; mm/h, median (range)	7 (2-45)	9 (2-85)	0.570
CRP; mg/dl, median (range)	0.2 (0.1-1.2)	0.2 (0.1-8)	0.781
Active disease, n (%)	5 (13.9)	16 (10.2)	0.554
Inactive disease, n (%)	6 (16.7)	19 (12.1)	0.423
Clinical remission on medication, n (%)	22 (61.1)	99 (63.5)	0.849
Clinical remission off medication, n (%)	3 (8.3)	23 (14.7)	0.422
Relapses, n (%)	12 (36.4)	45 (30.8)	0.541

JIA; Juvenile idiopathic arthritis, FGIDs; Functional gastrointestinal disorders, SD; standard deviation, RF; Rheumatoid factor, DMARDs; Disease modifying antirheumatic drugs, WBC; White blood count, ESR; Erythrocyte sedimentation rate, CRP; C-reactive protein.

DISCUSSION

In this study, we investigated the frequency of FGIDs' subtypes by applying Rome IV criteria with physician medical assessment and susceptibility factors related to FGIDs in children with JIA. Overall frequency of FGIDs was statistically higher than healthy control group. However, the frequencies of FGIDs subtypes were statistically similar between children with JIA and healthy control groups. When JIA patients divided into two groups in regard to presence of FGIDs, age at disease onset, diagnostic delay, disease duration, medication data, including corticosteroid treatment, clinical status of disease did not differ between the groups according to presence of FGIDs.

FGIDs represent a various combination of chronic or recurrent symptoms attributed to the gastrointestinal tract. The frequency of FGIDs is reported between 2.4 to 23% in children with different ethnicities[18,19] and even 34.6% in adult population[8]. These conditions cause repetitive physician visits and even hospitalizations with generally poor outcomes due to no obvious structural or biochemical explanation of pathophysiology[8]. With increased awareness of FGIDs, there are growing evidence on underlying pathophysiology. Given the higher rates of psychiatric comorbidities such as anxiety and depression in patients with FGIDs and vice versa suggests that FGID is a biopsychosocial disorder[20,21]. There is also an evidence that two-way axis between gut and brain play a role in FGIDs development by alterations of gut microbiota and immune homeostasis[9]. Additionally, studies have previously showed that, genetic factors, immune activation, infections, low-grade mucosal inflammation, and altered intestinal permeability are the pathophysiological mechanisms of FGIDs[9,10]. Because FGIDs consist of a group of heterogeneous diseases with heterogenous pathophysiology, it is difficult to design a treatment algorithm for all patients. Treatment choices include dietary modifications by increasing fiber intake, gluten-free diet, antispasmodic agents, intestinal secretagogues, ondansetron, opioids, antibiotics and probiotics, antidepressants and psychological therapies[7,10,22].

Besides, inflammatory bowel disease (IBD), such as

Chron's disease and ulcerative colitis, is determined by chronic inflammation in gastrointestinal tract, in which Th1/Th17 and atypical Th2 responses play roles in pathogenesis. There is considerable overlap between symptoms in patients with IBS and IBD. Because a substantial proportion of IBD patients have history of IBS diagnosis, it was suggested by some authors that IBS might be a state of mild, subclinical form of IBD[23,24].

Furthermore, gut microbiota has recently become one of the subjects of interest in JIA patients. Altered gut microbiota by dysbiosis, immune programming, microbe-specific systemic immune responses, and by local effects on mucosal integrity and intestinal immunity might predispose to JIA in children. Furthermore, children with JIA, particularly ERA and RF-positive subtypes, have an altered gut microbiota, with sharing some features of microbiota of patients with IBD[25]. Arthritis is one of the most frequent extraintestinal symptoms of IBD. Oligoarthritis and ERA subtypes of JIA are the most common chronic arthritis patterns that associated with IBD[26]. These findings together suggest in some points a shared pathogenesis between JIA, IBD, and IBS.

Thus, we wondered if children with JIA have increased frequency of FGIDs caused by maintenance of low-grade inflammation. We have found increased frequency of FGIDs in children with JIA in the present study. However, we could not find possible risk factors related to FGIDs development in JIA patients. All JIA patients did receive immunosuppressive drugs at any time before study enrollment which led us to think that the frequency of FGIDs might be reduced in our population due to prescribed anti-inflammatory drugs, such as corticosteroids and biologic agents. In order to evaluate the exact frequency of FGIDs and possible risk factors, further prospective studies including treatment-naive JIA patients are needed. As far as we know, this is the first study investigating FGIDs frequency and related possible risk factors in children with JIA. Therefore, we could not compare and generalize our results with another study including JIA patients. Additionally, a significantly higher prevalence of autoimmune disorders was demonstrated among patients with FGIDs in a large sample of adult patients in primary care[15]. Moreover, prevalence of FGIDs has been investigated in adult SLE patients in a more recent paper, in which a high prevalence of FGIDs was found in SLE women by utilizing Rome III criteria[14].

This study has several limitations, including the relatively low number of JIA patients and retrospective collection of patients' data. The other is that all JIA patients were taken immunosuppressive medication which might have reduced the frequency of FGIDs in those population.

Consequently, the frequency of FGIDs was higher in children with JIA compared with healthy children even during immunosuppressive treatments. Despite its several limitations our preliminary study is important to raise the awareness of pediatrician on this topic. Healthcare professionals should improve their awareness for FGIDs in children with JIA. Moreover, routine pediatric gastroenterologist evaluation could be a good option in JIA patients to diagnose those with FGIDs and manage this comorbidity by dietary modifications and psychosocial adjustments. Further prospective studies investigating FGIDs in treatment-naive JIA patients would expand our knowledge of FGIDs in those patients.

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