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ORIGINAL ARTICLE

Frequency of functional gastrointestinal disorders in children with familial Mediterranean fever

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Abstract

Introduction Familial Mediterranean fever (FMF) is characterized by self-limiting fever episodes usually accompanied by serositis, arthralgia, and arthritis. Functional gastrointestinal disorders (FGIDs) are diseases in which brain-gut axis and low-grade inflammation take part in pathogenesis. We aimed to study the FGIDs frequencies and possible risk factors for FGIDs in children with FMF.

Method This case-control study included 103 children with FMF followed up between July 2016 and July 2018 and 100 healthy controls. Age, gender, disease characteristics, and MEFV gene results were recorded retrospectively. Laboratory parameters were obtained at the time of study enrollment. Diagnosis of FGIDs was assessed with Rome IV criteria.

Results The mean age at study enrollment was 12.58 ± 3.79 and 9.71 ± 3.59 years in FMF and healthy control groups, respectively. Overall FGID frequency was 39.8% ($n = 41$) in FMF patients and 19% ($n = 19$) in the control group. Functional dyspepsia and irritable bowel syndrome (particularly constipation predominant subtype) rates were statistically higher in the FMF group. In detail, genotype, age at onset, symptoms, colchicine duration, and colchicine responses did not differ between FMF patients in regard to having FGIDs.

Conclusions This study showed that children with FMF may predispose to pain predominant FGIDs. We also suggest that FGIDs should be considered in FMF patients suffering recurrent abdominal pain episodes unaccompanied by APR elevation, which can be also named as incomplete FMF attacks.

Keywords Familial Mediterranean fever · Functional dyspepsia · Functional gastrointestinal disorders · Irritable bowel syndrome · Rome IV

Introduction

Mutations in Mediterranean fever (MEFV) gene result in the autoinflammatory disease called Familial Mediterranean fever (FMF), which is characterized by self-limiting fever episodes usually accompanied by serositis, arthralgia, and arthritis [1]. It is now accepted that mutant pyrin causes inflammasome activation and subsequent overproduction

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of Interleukin 1β [2, 3]. Colchicine is the mainstay in FMF treatment, which is known as effective in preventing febrile attacks and the most terrifying complication, secondary amyloidosis [4]. However, some patients suffer from abdominal pain despite prescribing the maximum tolerated colchicine. Sometimes, we just cannot be sure whether ongoing symptoms are due to colchicine resistance, lack of drug compliance, or presence of any comorbidities of gastrointestinal system.

Functional gastrointestinal disorders (FGIDs) are common causes of medical counseling and typically lack causative structural or biochemical disturbances of gastrointestinal system [5]. Beside it is formerly suggested that low-grade inflammation plays an important role on FGIDs pathogenesis, we recently showed that patients with a prior diagnosis of Henoch Schönlein purpura (HSP) had higher frequencies of overall FGIDs and its subtype, irritable bowel syndrome (IBS) [6, 7]. Since HSP is a well-known comorbidity of FMF, we also questioned if MEFV mutations influence FGID development.

Consequently, we suspected that an association between FMF and FGIDs may be present and particularly FMF may have a facilitating effect on FGID development by the low-grade inflammation hypothesis. Since FMF is the most common autoinflammatory disease worldwide and FGIDs are common health problems in childhood, it is necessary to distinguish if a gastrointestinal complaint is due to FMF or primary GI disorder in clinical practice. In this regard, the first attempt should be the determination of FGID prevalence among FMF patients. Therefore, we aimed to investigate the relevance between FMF and FGIDs in children with this study.

Material and methods

Patients

This study included 103 children with FMF, diagnosed in our department, followed up between July 2016 and July 2018, and accepted to participate the following procedures. Age at symptom onset, age at diagnosis, gender, symptoms, MEFV gene results, attack frequency before and under colchicine treatment, and colchicine dosage and duration were retrospectively obtained from medical files of the patients. Acute phase reactants (APRs) including erythrocyte sedimentation rate, C-reactive protein, and serum amyloid A were studied at the last visit, before the FGID assessment. The patients with elevated attack-free APRs were excluded from the study in order to distinguish an organic problem such as an FMF attack or subclinical systemic inflammation from the relevant functional problems. Complete response to colchicine was defined as complete cessation of inflammatory episodes in the presence of normal APRs [4]. Presence of red flag signs for organic gastrointestinal disorders such as chronic diarrhea, bloody stool, weight loss, significant vomiting, and family history of inflammatory bowel disease were the other exclusion criteria for the study enrollment [8]. The control group included healthy children, between 4 and 18 years of age, lacking any previous history of chronic health problems and aforementioned red flag signs for organic gastrointestinal disorders, who were admitted to hospital for well-child check-up. Informed consents were obtained from the parents of the patients prior to the study enrollment. The study was approved by Ethics committee of our Medical Faculty.

Assessment of functional gastrointestinal disorders

Diagnosis of FGIDs was assessed by questioning both parents and the patients with Rome IV criteria, which classify FGIDs in three sections: functional nausea and vomiting disorders, functional abdominal pain disorders (FAPD), and functional defecation disorders [8].

Functional dyspepsia (FD), a subclass of FAPD is defined as the occurrence of at least one of the following at least four times/month for the last 2 months: postprandial fullness, early satiation, epigastric pain, or burning not associated with defecation. Regarding another frequent FAPD, IBS diagnosis requires abdominal pain at least 4 days per month with one of the following criteria: relation with defecation, changes in frequency, and form of the stool plus permanent symptoms even after resolution of the constipation. In the case of insufficient criteria for FD and IBS, presence of episodic or continuous abdominal pain more than four times/month for the last 2 months lead to a diagnosis of functional abdominal pain (FAP). Furthermore, patients are diagnosed with functional constipation, the only defecation disorder throughout the study in the presence of at least two of the following criteria once per week for the last month and insufficient criteria for IBS; two or fewer defecations per week, fecal incontinence more than one time/per week, retentive posturing, painful or hard bowel movements, large fecal mass in rectum, and large stool diameter. It is necessary to obtain appropriate evaluation revealing the absence of another medical condition for all types of FGIDs [9].

Statistical analysis

Statistical analyses were performed using SPSS 20.0 statistical software package (IBM SPSS Statistics). Continuous variables were given as mean and standard deviation and as median and minimum-maximum where appropriate, thereafter analyzed between two groups with

Table 1 Demographic and clinical properties of 103 children with Familial Mediterranean fever

Parameters		
Age at diagnosis (median) (range)		6.31 (1.79–17.06) years
Age at disease onset (median) (range)		3.98 (0.25–16.02) years
Clinical manifestations	Fever, *n* (%)	90 (87.4)
	Abdominal pain, *n* (%)	95 (92.2)
	Arthralgia, *n* (%)	71 (68.9)
	Arthritis, *n* (%)	13 (12.6)
	Chest pain, *n* (%)	6 (5.8)
	Nausea, *n* (%)	11 (10.7)
	Diarrhea, *n* (%)	10 (9.7)
	Erysipelas like erythema, *n* (%)	9 (8.7)
	Splenomegaly, *n* (%)	3 (2.9)
	Prolonged febrile myalgia, *n* (%)	1 (0.9)
MEFV genotype	M694V/M694V	28 (27.2)
	M694V/other	20 (19.4)
	Other/other	55 (53.4)
Acute phase reactants at study enrollment	ESR (mm/h)	4 (2–20)
	CRP (mg/dl)	0.32 (0.1–1.51)
	SAA (mg/L)	3.14 (3–20)
Response to colchicine	Complete cessation of attacks	75 (72.8)
	Partial response (at least 50%)	21 (20.4)
	Non-responders	7 (6.8)
Duration of colchicine treatment (median) (range)		4.20 (0.50–13.68) years
Attack frequency before colchicine treatment per year (median, range)		12 (1–36)
Attack frequency under colchicine treatment per year (median, range)		0 (0–12)

ESR, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *SAA*, serum amyloid A; *MEFV*, Mediterranean fever

Mann Whitney *U* test. Categorical variables were expressed as numbers and percentages. Chi-square test was used to compare categorical variables between groups. The statistical level of significance for all tests was considered to be 0.05.

Results

Demographic features

This study included 103 patients (56 males, 47 females) with FMF and 100 healthy subjects (66 male, 34 female) between 4 and 18 years of age. The mean age at study enrollment was 12.58 ± 3.79 and 9.71 ± 3.59 years in FMF and healthy control groups, respectively.

Clinical findings

The most frequent clinical findings among FMF patients were as follows: fever 87.4% ($n = 90$), abdominal pain 92.2% ($n = 95$), arthralgia 68.9% ($n = 71$), arthritis 12.6% ($n = 13$), chest pain 5.8% ($n = 6$), diarrhea 9.7% ($n = 10$), nausea 10.7% ($n = 11$), erysipelas like erythema 8.7% ($n = 9$), splenomegaly 2.9% ($n = 3$), and prolonged febrile myalgia 0.9% ($n = 1$). MEFV gene sequencing was carried out for all patients, which revealed M694V mutation positivity in 48 (46.6%) patients, of which 28 was M694V homozygote. All patients were treated with colchicine, with complete response in 75 (72.8%) patients and non-responsive 7 patients also received canakinumab treatment. Demographic and clinical features are summarized in Table 1.

FGID assessment results

The frequencies of FGIDs and its subtypes among FMF and control groups are given in Table 2. At least one FGID diagnosis was made in 39.8% ($n = 41$) of FMF patients and 19% ($n = 19$) of the control group. More than one FGID was found in 14 (13.6%) and 4 (4%) of FMF and control groups, respectively. Although all FGIDs subtypes were more often in FMF patients than healthy subjects, only the differences were statistically significant for FD

Table 2 Demographic features and functional gastrointestinal disorders among patients with Familial Mediterranean fever and healthy controls

Parameters	Patients with FMF ($n = 103$)		Healthy controls ($n = 100$)		p
	n	%	n	%	
Gender (M/F)	56/47	54.4/45.6	66/34	66/34	0.115
FGIDs	41	39.8	19	19	*0.001*
More than one FGIDs	14	13.6	4	4	*0.024*
Functional dyspepsia	23	22.3	10	10	*0.022*
Irritable bowel syndrome	15	14.6	3	3	*0.005*
Diarrhea predominant	3	2.9	2	2	0.514
Constipation predominant	12	11.7	1	1	*0.003*
Functional abdominal pain	7	6.8	4	4	0.286
Functional constipation	10	9.7	4	4	0.165

FMF, Familial Mediterranean fever; *FGIDs*, functional gastrointestinal disorders

Significant *p* values are italicized

and IBS rates. In the terms of IBS subtype, constipation predominant IBS was significantly higher in the FMF group, whereas diarrhea predominant IBS were similar between these two groups. In detail, we examined whether genotype, age at onset, symptoms, attack frequency, and APRs at study enrollment and colchicine responses differ between FMF patients with or without FGIDs. However, there was no statistically significant difference in disease characteristics between these two groups (Table 3).

Discussion

Episodic abdominal pain usually lasting less than 72 h is often present with a frequency of 89.2–93.7% in the course of FMF [10, 11]. Acute peritonitis and small bowel obstruction due to sterile exudate in peritoneal cavity lead to the majority of abdominal pain and constipation in FMF [12]. However, sometimes it may be difficult to differentiate an FMF attack from organic GI disorders in which visceral inflammation is the cause of abdominal pain [13]. Moreover, FMF was previously linked to higher risk of inflammatory bowel disease (IBD) in several studies [14–16].

It was previously unclear whether MEFV mutations cause a loss of function or gain of function of pyrin [17]. Beside the hypothesis that pyrin had inhibitor effects on NLRP3 inflammasome, recent studies suggested that pyrin acts as a pattern recognition receptor and generates its own inflammasome activating caspase 1 and giving rise to Interleukin-1β (IL-1β) maturation with a NLRP3 independent pathway [2, 18, 19]. On the other hand, the pathogenesis of FGIDs still remains uncertain. Given the higher rates of FGIDs in patients with depression and somatic disorders, the vast majority data suggest that it is a biopsychosocial disorder [20, 21]. In addition to the studies enouncing brain-gut axis that includes the gut microbiota, neurons, and immune system, there is also a rising evidence of low-grade inflammation play role in the FGIDs pathogenesis. Because intestinal biopsies of IBS patients revealed inflammatory manner with higher IL-1β and Interferon-γ in a previous study, it is even postulated that FGIDs may represent a mild phenotype of IBD [6]. An earlier study showed that homozygote MEFV mutations were present in 20% of 59 children previously diagnosed with FAPD and recommended MEFV gene sequencing in Mediterranean populations with recurrent abdominal pain [22].

To the best of our knowledge, this is only the third study examining FGID prevalence and possible risk factors in FMF patients, also the first one in pediatric population. The first to introduce that functional constipation and diarrhea were more frequent in adults with FMF than healthy controls, while IBS and dyspepsia rates were statistically similar [23]. The other study only reported the IBS subtype in adult FMF patients and revealed statistically similar IBS rates between FMF patients and the control group [24]. Despite the conflicting results from these two previous adult studies, FGIDs were still worth researching in children with FMF due to the fact that inflammation plays a role in pathogenesis of both diseases. Hereby, we share that overall FGID, FD, and IBS (constipation predominant) rates were statistically higher in children with FMF than healthy controls in our study. Additionally, age at FMF onset, clinical properties and genotype, colchicine treatment duration, and response to treatment did not differ between patients in regard to the presence of FGIDs.

Subclinical inflammation was previously suggested to affect daily activities such as activity, sleep, and appetite in patients with FMF [25]. Although we are interested in the low-grade inflammation hypothesis in FGID development, patients with elevated APRs were excluded from this study to distinguish these complaints from overt GI disorders including FMF attack or IBD. For this reason, attack frequency and APRs at study enrollment did not differ between patients

Table 3 Demographic and disease characteristics of patients with familial Mediterranean fever according to the presence of functional gastrointestinal disorders

Parameters		FMF patients with FGIDs ($n = 41$)	FMF patients without FGIDs ($n = 62$)	p
Age at diagnosis, years (median, range)		6.15 (1.79–17.02)	6.53 (2.54–17.06)	0.093
Age at disease onset (median, range)		4.11 (0.41–16.02)	2 (0.25–11.8)	0.436
M964V positivity		24 (58.5%)	40 (64.5%)	0.342
M694V homozygosity		10 (24.4%)	18 (29%)	0.388
Clinical manifestations	Fever	36 (87.8%)	54 (87.1%)	0.584
	Abdominal pain	38 (92.7%)	57 (91.9%)	0.601
	Arthralgia	31 (75.6%)	40 (64.5%)	0.178
	Arthritis	3 (7.3%)	10 (16.1%)	0.155
	Chest pain	1 (2.4%)	5 (8.1%)	0.229
	Nausea	2 (4.9%)	9 (14.5%)	0.108
	Diarrhea	6 (14.6%)	4 (6.5%)	0.151
Acute phase reactants at study enrollment	ESR (mm/h)	6 (2–20)	4 (2–20)	0.369
	CRP (mg/dl)	0.30 (0.1–1.51)	0.32 (0.1–1)	0.906
	SAA (mg/L)	3.2 (3–20)	3.28 (3–6)	0.494
Complete response to colchicine		3 (11.5%)	13 (27.1%)	0.155
Duration of colchicine treatment, years (median, range)		4.31 (0.52–13.68)	4.08 (0.50–12.58)	0.240
Attack frequency before colchicine treatment per year (median, range)		12 (2–24)	12 (1–36)	0.413
Attack frequency under colchicine treatment per year (median, range)		0 (0–12)	0 (0–9)	0.288

ESR, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *SAA*, serum amyloid A; *FMF*, Familial Mediterranean fever; *FGIDs*, functional gastrointestinal disorders

Non-parametric Mann Whitney *U* test was performed while comparing quantitative data without normal distribution between the two groups

regarding to have FGIDs in our study. However, we think that our preliminary study will precede further studies investigating the associations between subclinical inflammation of FMF and FGIDs.

The other limitations of our study were the retrospective design, small number of patients, and the fact that all patients were under colchicine treatment. Although colchicine treatment controls majority of FMF symptoms and reduces the false positivity for FAPD born of FMF attacks, we cannot be sure whether colchicine has also a positive effect on FAPD or not. In this view, we also suggest that FAPD should be considered in FMF patients suffering recurrent abdominal pain episodes without APR elevation, which can be also named as incomplete FMF attacks.

In conclusion, we speculate that children with FMF may predispose to FGIDs, particularly FAPD regardless of colchicine treatment duration. Despite the lack of knowledge about FGID pathogenesis, further studies are needed to confirm our study. We may also recommend clinicians to be aware of FGIDs and consider relevant dietary and psychosocial adjustments in FMF management to avoid this comorbidity.

Compliance with ethical standards

Informed consents were obtained from the parents of the patients prior to the study enrollment. The study was approved by Ethics committee of our Medical Faculty.

Disclosures None.

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