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Original article

Esophageal motor function in Familial Mediterranean Fever: A prospective evaluation of motility in 31 patients

Mehmet Bektaş [a], Beyza Doğanay [b], Murat Alkan [a], Yusuf Ustun [a], Irfan Soykan [a,*]

[a] Ankara University Medical School, Ibni Sina Hospital, Department of Gastroenterology, 06100 Sihhiye, Ankara, Turkey
[b] Ankara University Medical School, Ibni Sina Hospital, Department of Biostatistics, 06100 Sihhiye, Ankara, Turkey

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ABSTRACT

Background: The aims of this study were to evaluate esophageal motor function in patients with Familial Mediterranean Fever (FMF) who had upper gastrointestinal symptoms and to compare esophageal motor function between FMF patients who developed amyloidosis and patients without amyloidosis.
Methods: 31 FMF patients with dyspeptic symptoms and 31 healthy age-matched individuals were included in the study. Endoscopic examination and esophageal motility testing were performed.
Results: Esophageal motor abnormalities were detected in 25.8% (8/31) of these patients [incomplete Lower esophageal sphincter (LES) relaxation: $n=4$, esophageal hypomotility: $n=2$, and hypotensive LES: $n=2$]. Median LES relaxation (%) (min–max) was significantly lower in patients with FMF compared to control group 94% (54–100) vs. 98% (80–100), $p=0.019$ respectively). However, mean LES pressure (mmHg) (19.5 ± 8.9 vs. 19.7 ± 5.6, $p=0.813$), duration of LES relaxation (s) (7.9 ± 1.7 vs. 8.7 ± 1.7, $p=0.068$), contraction amplitude of esophageal body (mmHg) (60.4 ± 23.3 vs. 58.2 ± 19.7, $p=0.691$) and median (min–max) peak velocity (s) [3.1 (−1.43–50.3) vs. 3.1 (0.9–8.7), $p=0.435$] were similar in patients with FMF compared to control group. There were no significant differences with regard to LES pressure, LES relaxation, LES relaxation duration, contraction amplitude (mmHg) and peak velocity (sc) among patients with FMF and amyloidosis, amyloidosis negative FMF patients and healthy controls.
Conclusions: Abnormal esophageal manometric findings can be observed at least in a subgroup of patients with FMF regardless of amyloid status. Investigation of esophageal motor function in patients with FMF who exhibit unexplained upper gastrointestinal symptoms between attacks may be a helpful tool in order to delineate esophageal motor dysfunction.

1. Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever and peritonitis, pleuritis, arthritis or erysipelas-like erythema. FMF has been described primarily in several ethnic groups originating in the Mediterranean littoral—Sephardic Jews, Armenians, Turks, North Africans, Arabs, and less commonly Greeks and Italians [1–4]. Among non-Ashkenazi Jews, Turks and Arabs from the East, the frequency of heterozygotes for MEFV, the gene responsible for FMF, is greater than 1/5 in general population [5–8]. Atypical attack consists of fever and serositis lasting from 1 to 4 days. Although it has been accepted that FMF patients are free of symptoms and appear healthy between attacks, some of the FMF patients experience other abdominal or digestive system manifestations, usually of prolonged or chronic nature, manifestations unrelated to the attacks such as irritable bowel syndrome or functional abdominal pain [9].

Esophageal manometry has not been systematically performed in patients with this particular disorder and no specific motility pattern has been attributed to the disease. We hypothesized that some of these above mentioned upper gastrointestinal (GI) symptoms may be the result of esophageal motor dysfunction. Therefore, the aims of this study were 1) to evaluate esophageal motor function, 2) to identify whether there was any specific motility pattern for patients with FMF who had upper GI symptoms without endoscopic abnormality, and 3) to compare esophageal motor function between FMF patients who developed amyloidosis and patients without amyloidosis.

2. Patients and methods

The study population consisted of 31 patients with FMF (9 patients are amyloid positive, diagnosed in rectal biopsy specimens), who were referred to the gastroenterology outpatient clinic due to dyspeptic symptoms, were enrolled into the study. The diagnosis of FMF was established according to the Tel Hashomer criteria [10]. Thirty-one healthy, age-matched individuals are also included in the study as a control group. None of the patients was on drugs that might alter esophageal motor function during motility testing. Patients entering the study were asked to complete a symptom questionnaire concerning the presence of heartburn, regurgitation, epigastric pain, nausea and vomiting. All patients had

* Corresponding author. Tel.: +90 312 508 2759; fax: +90 312 310 3446.
E-mail address: isoykan@medicine.ankara.edu.tr (I. Soykan).

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undergone upper GI endoscopic examination and esophageal motility testing in two separate days. Endoscopic examinations were performed by one of the investigators using a standard video gastroscope (Fujinon, Tokyo, Japan). Esophageal manometry was performed by using a single catheter containing 8 solid-state pressure transducers spaced at 5 cm intervals and attached to an online computer (MMS, Medical Measurement Systems, Netherlands). Patients came to the laboratory after at least 8 h of fasting. The 8-channel catheter was lubricated and passed nasally and advanced into the stomach. A slow station pull-through was performed at 1 cm increments. Once the lower esophageal sphincter (LES) was profiled, the distal pressure transducer which included four lumens was placed in the high-pressure zone of the LES, so that the proximal pressure transducers were located 5 cm, 10 cm, 15 cm and 20 cm above the LES. A series of 10 wet swallows (with 5 mL water bolus) were given at 30 s intervals. Each contraction was recorded and then analyzed by a computerized software system (MMS, Medical Measurement Systems, Netherlands) for amplitude, contraction and velocity. Lower esophageal sphincter relaxation and residual pressures were also recorded. The present study was approved by the Institutional Review Board of Ankara University Medical School and all patients signed informed consent before entering the study.

Statistical analysis was performed with SPSS 11.5 for Windows (SPSS Inc, Chicago, IL). Metric values were expressed as mean ± standard deviation (SD) and median (minimum–maximum). The differences between the groups were evaluated by Student's *t* test, one way ANOVA, Mann–Whitney *U* test and Kruskal Wallis test depending on the normality of the data. A *p* value less than 0.05 was considered as significant.

3. Results

Median age of the patients enrolled in the study ($n = 31$, 14 women) was 35.9 (range: 16–66) years. Median FMF disease duration was 12.8 years and 9 of the patients were diagnosed as having amyloidosis during the study. The clinical manifestations of FMF, endoscopic and manometric findings, and GI symptoms in our cases are summarized in Table 1. All patients in this study complained of upper GI symptoms, predominantly of heartburn and epigastric pain. Of the 31 patients who had undergone upper GI endoscopy, 4 patients had endoscopic abnormalities which consisted of esophagitis according to the Los Angeles classification (3 grade A, 1 grade B) [11]. Manometric investigation was abnormal in 8 patients (incomplete lower esophageal sphincter relaxations in 4 patients, esophageal hypomotility in 2 patients, and hypotensive LES in 2 patients). Of these 8 patients, four of them were suffering from heartburn and their endoscopic examination revealed grade A esophagitis in 2 of these patients.

As for manometric findings, median LES relaxation (%) was significantly lower in patients with FMF compared to the control group [94% (54–100) vs 98% (80–100), $p = 0.019$ respectively]. There were no significant differences between mean LES pressure (mmHg) (19.5 ± 8.9 vs. 19.7 ± 5.6, $p = 0.813$), mean LES relaxation duration (s) (7.9 ± 1.7 vs. 8.7 ± 1.7, $p = 0.068$), mean contraction amplitude (mmHg) (60.5 ± 23.3 vs. 58.2 ± 19.7, $p = 0.691$) and median peak velocity (s) [(3.1 (−1.43–50.3) vs. 3.1 (0.9–8.7), $p = 0.435$] in patients with FMF compared to the control group (Table 2).

Mean LES pressure (mmHg), median LES relaxation (%) and mean contraction amplitude (mmHg) were not statistically different in reflux positive FMF patients compared to reflux negative FMF patients [the presence of reflux disease was established according to Montreal definition [12]] (17.9 ± 8.7 vs. 20.5 ± 9.2 mmHg, 92% (88–96) vs. 88% (82–95), and 57.6 ± 28.0 vs. 62.2 ± 20.4 mmHg, respectively, p = ns, Table 3).

There were no significant differences with regard to mean LES pressure (19.3 ± 8.1 vs. 20.1 ± 11.3 vs. 19.9 ± 5.6, $p = 0.935$), median LES relaxation (%) [93.5 (65–100) vs. 95 (54–100) vs. 98 (80–100), $p = 0.058$)], mean LES relaxation duration (s) (8.0 ± 1.8 vs. 7.6 ± 1.5 vs. 8.7 ± 1.7, $p = 0.161$), mean contraction amplitude (mmHg) (58.9 ± 21.8 vs. 64.2 ± 27.4 vs. 58.3 ± 19.8, $p = 0.767$) and median peak velocity (s) [3.0 (−1.4–50.3) vs. 3.1 (2.5–3.8) vs. 3.1 (0.9–8.7), $p = 0.633$] among

Table 1
Clinical and laboratory features of patients with Familial Mediterranean Fever.

	n	%
Sex (female/male)	14/17	55/45
Tel Hashomer criteria		
Major criteria		
Recurrent febrile episodes accompanied by peritonitis, synovitis or pleuritis	31	100
Amyloidosis of the AA type without predisposing disease	9	29
Favorable response to continuous colchicine treatment	29	93,5
Minor criteria		
Recurrent febrile episodes	31	100
Erysipelas-like erythema	5	16
FMF in a first-degree relative	31	100
Symptoms		
Heartburn	12	38.7
Dysphagia	1	3.2
Noncardiac chest pain	1	3.2
Bloating	5	16.2
Epigastric pain	12	38.7
Endoscopic examination		
Normal	20	64.5
Sliding type hiatal hernia	6	19.3
Esophagitis	4	12.2
Barrett esophagus	1	3.2
Manometric findings		
Normal esophageal manometry	23	74.2
Incomplete lower esophageal sphincter relaxation	4	13.0
Hypomotile esophagus	2	6.4
Hypotensive LES	2	6.4

Table 2
Manometric findings in patients with FMF compared to control group.

	FMF patients ($n = 31$)	Healthy subjects ($n = 31$)	*p*
LES pressure (mmHg) (mean ± SD)	19.5 ± 8.9	19.7 ± 5.6	0.813[a]
LES relaxation duration (sc) (mean ± SD)	7.9 ± 1.7	8.7 ± 1.7	0.068[a]
LES relaxation (%) [median (min–max)]	94 (54–100)	98 (80–100)	0.019[b]
Peak velocity (sc) [median (min–max)]	3.1 (−1.43–50.3)	3.1 (0.9–8.7)	0.435[b]
Contraction amplitude (mmHg) (mean ± SD)	60.5 ± 23.3	58.2 ± 19.7	0.691[a]

LES: Lower esophageal sphincter. FMF: Familial Mediterranean Fever.
[a] *p* value was based on Student's *t* test.
[b] *p* value was based on Mann Whitney *U* test.

Table 3
Manometric findings in patients with reflux symptoms compared to patients without reflux symptoms.

	Reflux negative ($n = 19$)	Reflux positive ($n = 12$)	*p*
LES pressure (mmHg) (mean ± SD)	20.5 ± 9.2	17.9 ± 8.7	0.593[a]
LES relaxation duration (sc) (mean ± SD)	7.6 ± 1.5	8.0 ± 1.8	0.332[a]
LES relaxation (%) [median (min–max)]	88%(82–95)	92% (88–96)	0.072[b]
Peak velocity (sc) [median (min–max)]	5.7 (0.5–10)	2.5 (1.7–3.4)	0.170[b]
Contraction amplitude (mmHg) (mean ± SD)	62.2 ± 20.4	57.6 ± 28.0	0.496[a]

LES: Lower esophageal sphincter.
[a] *p* value was based on Student's *t* test.
[b] *p* value was based on Mann Whitney *U* test.

Table 4
Comparison of esophageal manometric findings in amyloid negative, amyloid positive patients and healthy subjects.

	Amyloid negative patients ($n=22$)	Amyloid positive patients ($n=9$)	Healthy subjects ($n=31$)	p
LES pressure (mmHg) (mean ± SD)	19.3 ± 8.1	20.1 ± 11.3	19.9 ± 5.6	0.935[a]
LES relaxation duration (sc) (mean ± SD)	8.0 ± 1.8	7.6 ± 1.5	8.7 ± 1.7	0.161[a]
LES relaxation (%) [median (min–max)]	93.5 (65–100)	95 (54–100)	98 (80–100)	0.058[b]
Peak velocity (sc) [median (min–max)]	3.0 (−1.4–50.3)	3.1 (2.5–3.8)	3.1 (0.9–8.7)	0.633[b]
Contraction amplitude (mmHg) (mean ± SD)	58.9 ± 21.8	64.2 ± 27.4	58.3 ± 19.8	0.767[a]

LES: Lower esophageal sphincter.
[a] p value was based on one way ANOVA.
[b] p value was based on Kruskal Wallis test.

patients with amyloidosis, without amyloidosis and healthy controls (Table 4).

4. Discussion

In our study, 31 FMF patients with upper gastrointestinal symptoms were evaluated. Esophageal motor abnormalities were detected in 25.8% of these patients with manometric investigation; and 12.9% of these patients had endoscopic findings. When manometric findings of FMF patients are compared with healthy control group, there were no significant differences between lower esophageal sphincter pressure and contraction amplitude in the body of the esophagus.

Some systemic diseases that have progressive evolution can affect several organs, including the esophagus, resulting in secondary esophageal disturbances such as connective tissue disorders and neurological diseases [13]. The effect of FMF on esophageal motor function is not fully investigated. It has been shown that in patients with primary and/or secondary amyloidosis, deposition of amyloid protein in the smooth and striated muscle as well as in the enteric nervous system causes motor dysfunction of the esophagus [14]. Rubinow et al. studied esophageal manometry in 24 patients with primary amyloidosis and six patients with secondary amyloidosis. Resting lower esophageal sphincter pressure was decreased in 12 patients with primary amyloidosis and two with secondary amyloidosis; 12 of these 14 patients complained of heartburn. Abnormalities in the motility of the body of the esophagus were found in nine patients with primary amyloidosis and one with secondary amyloidosis [15]. Another esophageal manometric study had been performed in eight patients with familial amyloid polyneuropathy. All eight patients had an abnormality of the lower esophageal sphincter. Seven of eight had a borderline or decreased lower esophageal sphincter pressure and the other patient had a non-relaxing lower esophageal sphincter pressure. Six of eight patients exhibited abnormalities in the body of the esophagus consisting of either simultaneous or decreased amplitude of contractions involving the smooth or striated muscle or both [14].

In our study, secondary amyloidosis was found in 29% (9/31) of FMF patients. Abnormalities in the motility of the body of the esophagus and lower esophageal sphincter pressure were found in 3 (33.3%) patients with amyloidosis (incomplete lower esophageal sphincter relaxation in 1 patient, esophageal hypomotility in 1 patients, and hypotensive LES in 1 patient). However, esophageal motor abnormalities were found in 5 (23.8%) of the amyloid negative FMF patients. Although amyloidosis can be a cause of motor disorders of the esophagus, such as achalasia [16,17], in our study we did not observe such a specific motor abnormality in any of the patients.

In the current study, esophageal symptoms like heartburn ($n=12$), chest pain ($n=1$), and dysphagia ($n=1$) were found in 14 of 31 patients with FMF. Reflux symptoms (heartburn) were more common in amyloid positive FMF patients (55.6%) compared to amyloid negative FMF patients (31.8%). Abnormal esophageal motility pattern was observed in 4 cases and all of them had reflux symptoms. Although infiltration of the esophagus by amyloid protein has not been investigated in this study, amyloid positive and negative patients did not show different patterns of esophageal motor function.

In conclusion, abnormal esophageal manometric findings can be observed at least in a subgroup of patients with FMF regardless of amyloid status. Investigating esophageal motor function in FMF patients who exhibit unexplained upper GI symptoms between attacks may be a helpful instrument in order to show esophageal motor dysfunction. Therefore, further prospective, well-designed studies may shed some light on the pathophysiology of esophageal motor dysfunction in patients with FMF.

Learning points

- Abnormal esophageal motor function can be observed in some of the patients with Familial Mediterranean Fever regardless of amyloid status.
- Investigation of esophageal motor function in patients with Familial Mediterranean Fever who exhibit unexplained upper gastrointestinal symptoms between attacks may be a helpful tool in order to delineate esophageal motor dysfunction.

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