

**Assessment of the problem and the main
determinants of incorrectly performed laparotomies
in FMF patients with abdominal attacks in Yerevan,
Armenia A qualitative study**

**Master of Public Health Thesis Project Utilizing Professional Publication
Framework**

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Abbreviation List

AAP	-	Acute abdominal pain
AUA	-	American University of Armenia
ED	-	Emergency department
ESR	-	Erythrocytes Sedimentation Rate
DL	-	Diagnostic laparoscopy
FGD	-	Focus group discussion
FMF	-	Familial Mediterranean Fever
FPP	-	Familial paroxysmal polyserositis
PCT	-	Procalcitonin

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Abstract

Background: Familial Mediterranean fever (FMF) is an autosomal recessive inherited disease characterized by recurrent attacks of fever and pain secondary to polyserositis, mainly of the abdomen and joints. The symptoms start abruptly, occur before the age of 20 in 90% of the patients and generally decrease spontaneously within 1-4 days. Because of similar clinical and laboratory settings, it is difficult to differentiate an attack of FMF from acute appendicitis and other acute abdominal conditions. Therefore preoperative evaluation is very important to prevent unnecessary surgeries in FMF patients with abdominal attacks.

Objective: This study aims to describe the situation regarding incorrectly performed laparatomies for acute abdomen among FMF patients with abdominal attacks in Yerevan, Armenia. It further aims to assess potential contributing factors to the incorrectly performed laparatomies in these patients.

Methods: Cross-sectional conventional content analysis approach was employed for the proposed study to gain deep insights into the study questions. Qualitative study design was used to conduct in-depth and focus group interviews with the health care providers (surgeons, physicians who deal with the FMF patients in general and rheumatologists and FMF patients who had surgeries), to understand their experience in this field. In-depth interviews with FMF patients who had undergone surgery (laparotomies/laparoscopies) helped us identify the scope of the problem and reveal patients' experience within the health care system.

Results: Two focus groups with surgeons and thirteen in-depth interviews with six health care providers (experts) and seven FMF patients who had undergone surgeries were completed. Three prospective focus group members refused to participate due to lack of time. Five surgeons participated in both focus group discussions. All participants were males. Work experience varied between 8 and more than 30 years. Age varied between 27 to 63 years old. Among physicians who deal with FMF patients in their practice all experts were females except for two. Work experience varied from 8 to 35 years and the age range was from 35 to 67 years old. Among FMF patients, who underwent surgeries before their disease was diagnosed, 4 were females and 3 were males. The age range varied between 23 and 62 years.

Eight categories were revealed from in-depths interviews and focus group discussions that describe the proposed research questions. The main categories are (1) Causes of the acute abdomen (2) Acute abdominal pain in FMF patients (3) First experience of FMF patients in medical settings and potential contributing factors to misdiagnosis (4) Diagnosis of FMF abdominal pains vs. acute abdomen of other causes (5) Management of acute abdominal pains/FMF abdominal attacks (6) Changes in practice (7) Patients' attitude towards unnecessary surgeries (8) Participants' further suggestions.

Conclusion: The study findings revealed that situation in Armenia regarding FMF patients who had undergone surgeries due to misdiagnosis is more satisfactory than we expected. It was explained that as Armenia is considered an endemic zone for FMF so the doctors, especially in the Yerevan, are more informed about the disease and they very often can differentiate FMF abdominal attacks from other causes. However, there is still misdiagnosis of FMF abdominal attacks. So, we developed an algorithm for differential diagnosis of acute appendicitis and FMF abdominal attacks which will help surgeons avoid misdiagnosis and unnecessary surgeries in FMF patients and also not miss acute appendicitis in these patients.

Introduction

Background and Significance

Background

Familial paroxysmal polyserositis (FPP) or Familial Mediterranean fever (FMF) is an autosomal recessively inherited disorder (1). It is manifested by recurrent episodes of fever accompanied by signs of peritonitis, pleuritis and synovitis and sometimes complicated by amyloidosis (1). In general the disease is caused by mutations in a single MEFV gene {Sarkisian, 2005 4 /id}. Despite this, it is possible that other genes mutations and/or environmental factors are involved in the etiology {Armenian, 1982 1 /id}.

Prevalence

FMF is most common in the populations of Mediterranean descent: Armenians, Jews, Arabs, and Turks. Data reported between 1954 and 1977 showed that about 50% of diseased people were Armenians, 32% were Jewish, 8% were Arabs, and the remaining were other nationalities (4). For Armenians the prevalence rate varies depending on their location. It is 100 per 100,000 for Armenians in Lebanon compared to 200 per 100,000 for Armenians living in Fresno County, California {Khachadurian, 1974 2 /id;Schwabe, 1974 11 /id}. The prevalence rate of FMF among Armenians living in Yerevan is estimated to be 1 per 100 (3). According to the data from Center of Medical Genetics and Primary Health Care the rate of carriers of MEFV gene mutations in Armenians was very high (1:5) and similar to North African and Iraqi Jews, Turks, but lower than in Ashkenazi Jews (1:4.5), Moroccan Jews (1:3.5) and Muslim Arabs (1:4.3) (6). From 2003 to 2005 several cases of the disease have been reported in Italian and Greek patients as well as in populations of non-Mediterranean descent {Gkretsi, 2009 69 /id;La, 2003 7 /id}.

The literature consistently indicates that FMF is more prevalent among male gender and the ratio ranges between 1.5 to 2.0:1.0 (2;8;9). However, there are studies which have revealed greater difference between male and female gender. For instance, a study conducted by Khachadurian and Armenian (1974) in 120 cases from Lebanon found male to female ratio of 7:3 (1).

Clinical Characteristics of FMF attacks

The onset of the disease varies among patients. Almost 50 % of cases experience their first attack during the first decade of life. By the age 20 years about 90 % of patients have already had their first attack and only in 5 % of cases it manifests after the age 30 years (2;10;11).

FMF is characterized mainly by recurrent, self-limited episodes of fever and inflammation of synovial and serous surfaces, mainly of the peritoneum (episodes of sterile peritonitis, pleuritis) and joints (arthritis) (12-14), rarely erysipeloid erythema, pericarditis, acute orchitis and protracted febrile myalgia (15;16) and tunica vaginalis (16). Fever is one of the main symptoms of FMF attacks, but sometimes it can be unnoticeable. It usually increases up to 38⁰-40⁰C and can be followed by chill (15). Abdominal attacks begin suddenly, usually without a recognizable precipitating event and last for 6 to 72, or, rarely, for up to 96 hours (15). Nearly 95% of people with FMF experience abdominal pain during their attacks (14;17). It may be diffused or localized, and varies in intensity from mild, without overt signs of peritonitis, to the more typical severe pain, which requires bed rest (18). Findings on physical examination are distension of the abdomen, rigidity, direct and rebound tenderness and reduced peristaltic sounds (19) which resemble acute abdomen (8;20). The recurrent peritonitis very often can lead to peritoneal adhesions and intestinal obstructions that also imitate surgical abdomen (21). The second common symptom of FMF is joint pain. However, among Armenians and Japanese, pleuritis is more prevalent than arthritis (22). The prevalence of skin rash (erysipelas-like erythema) is much lower in all of the studied FMF

populations (23). The fact that the disease manifestation may be different among different individuals or may change its course over the patient's lifetime has been observed among populations of various ethnic origins (23). Comparison of different populations showed that fever and peritonitis were present in more than 90% of the patients (23).

Diagnosis of FMF

The diagnosis of FMF is clinical since there is no specific imaging or laboratory tests, other than a molecular genetic test that is not widely available. Many authors suggested many different types of clinical diagnostic criteria (14;24;25). The first diagnostic criteria was set by Siegel in New York in 1945 and the next followed in 1948-49 by Riemann from the American University of Beirut, however, the clinical diagnosis for a long time was based on the Heller's group developed in 1955 (1;5;16;24). The criteria have been widely used for many years (10). Armenian summarized FMF diagnostic criteria as follows: 1. a minimum of 4 attacks of peritonitis or pleuritis, or both lasting from 24 to 72 hours manifested sometimes by arthritic attacks and accompanied by fever, 2. absence of any symptoms between the attacks, and 3. absence of any etiologic or pathologic factor capable of explaining the clinical picture (5).

Tel Hashomer diagnostic criteria for FMF were proposed in 1997 (2;12;24): They have been widely used for the diagnosis of familial Mediterranean fever. They include two categories: major and minor criteria, classified as follows: *Major criteria* include recurrent febrile episodes accompanied by serositis, amyloidosis of AA-type without a predisposing disease, and favorable response to continuous colchicine treatment.

Minor criteria are recurrent febrile episodes, erysipelas-like erythema, and Familial Mediterranean fever in a first-degree relative.

According to the authors who proposed and validated the clinical criteria, the clinical diagnosis should have the central role in diagnosing FMF. The authors suggest that only

molecular diagnosis misses up to 20 % of patients with clinical FMF (26). According to another group, however, a number of patients with clinical FMF according to the Tel-Hashomer criteria (24) might not have their clinical manifestation resulted from mutations in MEFV gene, but from an unknown locus (22). The likelihood of clinical diagnosis of FMF depends on the population, its homogeneity, and the number of screened mutations. Molecular testing is mostly used for confirmation of the diagnosis, diagnostic testing, testing of carriers, and prenatal diagnosis. Laboratories perform targeted mutation analysis for the common mutations in exons 2, 3, and 10 of the MEFV gene and/or sequence analysis of selected exons, most frequently exon 10 (27).

Acute Abdomen and its main causes

According to Deaver, acute abdomen is “any acute intra-abdominal trouble that requires urgent surgical treatment” (28). It is a condition which is produced by the inflammatory, obstructive, or vascular mechanisms and manifested by sudden onset of abdominal pain, gastrointestinal symptoms and varying degrees of local and systemic reaction (28-31). It is an episode of severe abdominal pain that lasts for several hours or longer and requires urgent medical attention (32). Usually acute abdomen starts with the focal pain and tenderness, and then progresses becoming more generalized. In certain situations, causes of abdominal pain can vary from severe life-threatening conditions to more benign underlying conditions (32-34). The main causes of acute abdominal pain (AAP) requiring urgent treatment may be summarized as follows: acute appendicitis, abdominal aorta aneurysm, hollow viscera perforation, obstructed intestine with or without strangulation, intestinal ischemia, cholecystitis and acute cholangitis, rupture of ectopic pregnancy, intra-abdominal abscess, hepatic rupture, ruptured spleen and extra-abdominal pathology (35;36).

Differential diagnosis of FMF attacks vs. surgical diseases that lead to acute abdomen

Determining the cause of abdominal pain in FMF patients is a challenging task (21). For instance, if a patient is diagnosed with FMF, physicians may tend to relate each episode of abdominal pain to a FMF attack while that may not always be the case. Abdominal pain in FMF patients might be a sign of other conditions. For example, according to a report by S. Akar et al, FMF abdominal attacks and other clinical manifestations of FMF attacks such as fever, malaise, loss of appetite, the presence of pleuritic chest pain or arthritis associated with abdominal pain in some Turkish patients can be coincide with the perimenstrual attacks (37). In other cases, abdominal pain can be a symptom of other serious co-morbidity, such as appendicitis or intestinal obstruction which requires an urgent intervention (8;38). A delay in decision to perform laparotomy in these cases can result in grim consequences such as perforation, abscess formation, or development of peritonitis (30). Therefore, it is suggested that every single abdominal pain should be considered independent from others even if a patient has been diagnosed with FMF (39). On the other hand, acute abdominal attacks in FMF can mimic appendicitis or other abdominal organs' inflammation that lead to an acute abdomen (18). As a result, many patients with undiagnosed FMF have appendectomies or other exploratory surgeries of the abdomen especially if they present with fever and abdominal pain as the only symptoms (18). Other diseases resembling acute abdomen that do not need urgent interventions are porphyria, FMF, hemorrhagic vasculitis, Henoch Schonlein etc. (40). Correspondingly the course of action would be different depending on the etiology symptoms of acute abdomen. This makes the differential diagnosis particularly important (32;34;40;41).

It may be difficult to differentiate FMF attack from surgical acute abdominal especially acute appendicitis due to similar symptoms and laboratory findings (17;42).

Although elective appendectomy may prevent the risk of misdiagnosis and unnecessary emergency operations, it is not recommended by many clinicians (8;14;18;37). Elective appendectomy does not exclude other causes of acute peritonitis and may cause peritoneal adhesions and fibrotic bands (9;14). A careful medical history might be helpful in preventing unnecessary surgeries in FMF, since abdominal attacks in FMF patients typically resolve spontaneously in 1 to 4 days (39).

Laboratory indicators are not very helpful in differential diagnosis of FMF attacks, since they are consistent with non-specific inflammation: elevated erythrocyte sedimentation rate, white blood cell count, as well as acute phase proteins produced by liver, such as C reactive protein, fibrinogen, serum amyloid A and others (43). According to the data of a study conducted in Turkey the average gap between disease onset and diagnosis of FMF was approximately 6.9 years (37), which correspondingly may lead to unnecessary abdominal operations. However, even with the best clinical judgment, laboratory testing, and imaging, the actual diagnosis of a patients' abdominal pain remains ambiguous in more than 40% of cases (48). In this respect preoperative radiological evaluation becomes very important to prevent unnecessary surgical approach in FMF and may be helpful for accurate diagnosis and treatment (8). Also the accuracy of the diagnosis depends on the radiologist (44;45). Ultrasonography is most preferred diagnostic radiological tool as it has low cost and also widely available (8;44). However, it has its disadvantages; obesity, abdominal tenderness, increased bowel gas, and guarding may cause difficulties for accurate diagnosis (44;46). A study conducted recently by B. Kisacik et al showed that procalcitonin (PCT) could be a useful test in the differentiation of FMF attacks from acute appendicitis (38).

The extent of the problem in different ethnic groups

In 2007 in the United States, abdominal pain was the chief complaint of over 6.5% patients presenting to an emergency department (ED), among whom 65% were female, and from

them 24.7% were hospitalized, and 21% diagnosed with undifferentiated abdominal pain (47). According to the US data, overall about 20% to 25% of patients presenting with acute abdominal pain are found to have a serious condition requiring hospital admission (48). On initial assessment, the emergency physician attempts to sort out patients who have immediately life-threatening diseases from those who may have more benign causes for their abdominal pain (49). Acute abdomen requires urgent treatment, often including emergency operation (50). The urgency usually precludes prolonged investigation. There are few specific tests or examinations, which may be relied upon to give clear answers as to the exact cause of the acute condition (1;49;50). In these circumstances imaging studies are useful for prompt and accurate diagnosis (39). According to the literature, often misdiagnosis lead to unwanted complications such as unnecessary laparotomies, rupture of appendixes, peritonitis local or generalized, abscesses and other complications (31). As was mentioned above an acute appendicitis is the most common cause of an acute abdominal pain that requires surgical treatment (36;51). Different studies investigated the rate of unnecessary appendectomies (31;38;52). According to some studies, there is approximately 6% to 7% lifetime risk of appendicitis in adolescents and young adults in general population (36;52;53). According to another study surgical operations were performed in 551 patients (47%), 16% of which were unnecessary appendectomy (33). Other studies have recorded an incidence of unnecessary appendectomy ranging from 8 to 33 per cent again among young adults (13). The frequency of appendectomy in a nationwide multicenter study evaluating 2838 Turkish FMF patients was 19% (54). The prevalence of appendectomy in FMF patients was found to be 4.8% in Turkey (55), 9.0% in Israel (real acute appendicitis was 5% based on the appendectomy material reexamination) (54). So, different studies show that the rate of appendectomies in FMF patients is higher than that in not FMF patients (42;54).

Situation in Armenia

FMF very common among Armenian population and today more than 30,000 FMF patients in Armenia are registered with high prevalence (1:5) in high landed regions (3;22). According to different studies the prevalence rate among Armenians varies from 1 per 200 to 1 per 1000. The prevalence rate of FMF among Armenians living in Yerevan is estimated to be 1 per 100 (3). According to the Center of Medical Genetics and Primary Health Care, 2,611 out of 14,500 (18%) FMF patients had undergone surgeries. There is lack of available data does not allow the real picture of the problem in Armenia.

Moreover due to high cost of unnecessary surgeries, as well as medical complications, it is critical to understand the extent of the problem of unnecessary surgeries in Armenian FMF patients. This study aims to describe the situation regarding incorrectly performed laparatomies for acute abdomen among FMF patients with abdominal attacks in Yerevan, Armenia. It further aims to assess potential contributing factors to the incorrectly performed laparatomies in these patients.

It is important to evaluate the knowledge and attitudes of FMF patients and physicians who diagnose and treat FMF patients towards unnecessary surgeries and the entire diagnostic process of FMF. The results of these analyses will be helpful for the development of a diagnostic algorithm in future that can act as a guideline for physicians to evaluate patients with acute abdominal FMF attacks.

More specifically, the study objectives are:

- ✓ To explore the experiences of FMF patients in health care settings with regard to diagnosis and treatment of FMF in Armenia. In particular, describe patients' journey as they first get in contact with the health care system to the time of diagnosis and treatment.
- ✓ To understand the impact of unnecessary surgeries on FMF patients.

- ✓ To understand the diagnostic criteria and differential diagnosis for acute abdomen used in surgical settings in Armenia
- ✓ To assess FMF patients' and health care professionals' knowledge about FMF abdominal attacks
- ✓ To identify the experience of health care providers concerning FMF abdominal attacks and understand their beliefs and attitudes towards the FMF abdominal attacks diagnosis and management.

Methods

Justification of the Study design

Cross-sectional conventional content analysis approach was employed for the proposed study as we aim to gain deep insights into the study questions. Qualitative study design allowed us to conduct in-depth and focus group interviews with the health care providers (surgeons, physicians who deal with the FMF patients in general and rheumatologists and FMF patients who had surgeries), to understand their experience in this field and identify the key determinants that let surgeons perform surgeries on patients with acute abdomen. In-depth interviews with FMF patients who had undergone surgery (laparotomies/laparoscopies) helped us identify the scope of the problem and reveal patients' experience within the health care system. This research helped to identify the gaps in current situation in Yerevan regarding FMF patients who had undergone surgeries and understand patients' and doctors perspectives regarding necessity of such surgeries. These diverse data sources provided textual data that was analyzed using conventional content analysis. The final product of the project has explored the scope of FMF misdiagnosis in Armenia, has revealed health care providers' attitudes and beliefs towards this problem and helped to identify problem solutions and also develop a decision tree for

differential diagnosis of FMF acute abdominal pains and acute appendicitis which will improve FMF diagnosis and care.

Convenience sampling approach was used to recruit participants.

Population

FMF patients

Armenian FMF patients living in Yerevan aged 18 and over who had undergone surgery due to an acute abdomen were eligible for the study. The eligible patients were identified by searching the database at the Centre of Medical Genetics and Primary Health Care, the main referral center of FMF patients from all over Armenia. The center physicians informed FMF patients who had undergone surgeries about the study. After getting the agreement to participate, the student investigator interviewed them in the Center of Genetics and Primary Health Care.

Health care providers

In-depth interviews and focus-group discussions were conducted with health care providers who had experience with FMF patients. Focus group discussions were held with the surgeons from two largest inpatient facilities in Yerevan, “Erebuni” and “Armenia” Medical Centers who were invited to participate at their convenience. In-depth interviews were conducted with the physicians who deal with FMF patients in their everyday work. After participants’ informed consent was obtained, semi-structured interview/focus group discussion guide was administered. During in-depth interviews and focus group discussions short socio-demographic form was distributed to the physicians that did not contain any identifiable information.

Human Subjects Protection

The study was approved by the Institutional Review Board of the American University of Armenia. All participants provided oral informed consent. Interviewees were informed about anonymity and confidentiality of the interviews and their right to stop their participation at any time during the data collection process. Participants were reminded not to use names or other identifiers during interviews. Audio-recording was used to document the data. All participants, save one, consented to audio-recording. The study is done in collaboration with the Center of Medical Genetics and Primary Health Care (Appendix 1).

Data Collection, Management, Analysis and Rigor

For the proposed study the data were collected through in-depth interviews and focus group discussions with open-ended questions (Appendix 2). Focus group discussions were held with the surgeons and in-depth interviews with physicians and patients. Interview guides were developed in a semi-structured format to address the aims of the study. Semi-structured approach to data collection was chosen in order to focus each interview session on particular topic areas while providing an opportunity for broader participant insights to be expressed during the course of the dialogue. Interview guides were developed in a semi-structured format to address the aims of the study. Probes were open-ended and reflected participants' comments to develop their comments further.

One of the focus group discussions was conducted at the American University of Armenia (AUA) by the student investigator and the other one was conducted in the 'Armenia' Medical Center. In-depth interviews with physicians were conducted at their workplaces. In-depths interviews with FMF patients were conducted in the Center of Medical Genetics and Primary Health Care. Only one participant did not permit audio-recording of interviews. However, she was interviewed and the notes were used for the data analysis. Data were collected in these interviews by the student investigator who simultaneously took

notes during the interviews and then transcribed and detailed these notes immediately after each interview. All recorded interviews were taped, transcribed and translated from Armenian to English.

All transcribed data were read carefully, highlighting words, key words, and phrases that seemed to be relevant to the research question. After interviews during coding and seeking initial confirmation of the ideas in the narratives of the participants, specific codes emerged and were categorized. Some categories were collapsed and others identified as subcategories of more dominant codes. Definitions of categories and subcategories were developed and confirmed in review of codes. Specific codes within categories were reviewed to insure reliability and truthfulness. Data saturation was achieved in all major categories. Analysis concluded with organization of categories and subcategories into a hierarchical structure to describe the situation in Armenia regarding incorrectly performed surgeries in FMF patients due to the abdominal attacks and determine the potential contributing factors that led to these surgeries. The analyses are used as a foundation to posit possible solutions and improvements in health care of FMF patients with abdominal attacks. Triangulating the perspectives of participants and the format for data collection enhanced rigor in both data collection and analysis.

Results and discussion

Two focus groups with surgeons and thirteen in-depth interviews with six health care providers (experts) and seven FMF patients who had underwent surgeries were completed.

Focus Groups

Three prospective focus group members refused to participate due to lack of time. Overall 10 surgeons participated in two focus groups, five participants in each. All

participants were males. Work experience varied between 8 and more than 30 years. Age varied between 27 to 63 years old.

In-depth interviews

The physicians from “Armenia” Medical Center, Center of Medical Genetics and Primary Health Care, №1 Clinical Hospital, who care for FMF patients in their everyday work, were interviewed about their experience concerning acute abdomen and FMF abdominal attacks. Physicians who took part in the study were interviewed at their work places and were chosen by convenience and availability. Among physicians who deal with FMF patients in their practice all experts were females except for two. Work experience varied from 8 to 35 years and the age range was from 35 to 67 years old.

Among FMF patients, who underwent surgeries before their disease was diagnosed, 4 were females and 3 were males. The age range varies between 23 and 62 years. It was possible to interview 7 FMF patients with surgeries from whom 4 were females and 3 males. They were interviewed by the student investigator in the Center of Medical Genetics and Primary Health Care during their routine visits to their physician. They were informed about the study by their physician and after getting agreement they were interviewed.

Main Findings

Eight categories were revealed from in-depths interviews and focus group discussions that describe the proposed research questions. The main categories are (1) Causes of the acute abdomen (2) Acute abdominal pain in FMF patients (3) First experience of FMF patients in medical settings and potential contributing factors of misdiagnosis (4) Diagnosis of FMF abdominal pains vs. acute abdomen of other causes (5) Management of acute abdominal pains/FMF abdominal attacks (6) Changes in practice (7) Patients’ attitude towards unnecessary surgeries (8) Participants’ further suggestions. Based on the main findings about

the FMF abdominal pain and the diagnostic criteria, we developed a decision tree for differentiation between FMF acute abdominal attacks and acute appendicitis.

Causes of the acute abdomen

Acute abdomen is the final diagnosis of a disorder occurred in the abdomen by the inflammation of a peritoneum and may mask the clinical manifestation and cause difficulties in identifying the real cause by the generally performed diagnostic methods. According to the surgeon responders, acute abdomen is a symptom-complex and could be either of surgical origin or of therapeutical, non-surgical origin. Moreover, some of the surgeons argued that acute abdomen is not a diagnosis; rather, it is a condition caused by inflammation of the abdominal organs and the peritoneum. In certain situations, causes of abdominal pain can vary from severe life-threatening symptoms, disease processes, to more benign underlying conditions (32-34).

“It is difficult to diagnose acute abdomen as there are many surgical and therapeutic etiological factors that can lead to it, and the physician should be very careful not to miss the symptoms that are common for such kind of disease.”

FGD1 P3

“The acute abdomen isn’t a diagnosis it is a symptom-complex and includes many symptoms, which very often caused by the peritonitis for what we diagnosed as an acute abdomen.”

FGD 2 P 4

The study findings showed that FMF abdominal attacks are very often confused with those serious conditions that need surgical intervention as the symptoms and manifestations are similar to each other, a phenomenon also described in the literature (8;21;38). The most common cause of acute abdomen, as stressed by all surgeons, is appendicitis. Cholecystitis, hernia of the bowel, perforation of the ulcer was mentioned by participants as other common

causes of acute abdomen. Some causes of abdominal pains, such as heart failure, chest organs' disorders, and gynecological disorders, do not need surgical intervention. The physicians stated that some systemic diseases like Henoch Schonlein purpura or hemorrhagic vasculitis, FMF can also lead to acute abdominal pains that mimic acute abdomen. Thus if a patient presents with acute abdominal pain, the surgeons or emergency physicians should consider all serious conditions that require urgent solutions, but at the same time should think about the those that do not need surgical interventions (FMF attacks) and should not hurry to operate the patient.

Acute abdominal pain in FMF patients

FMF is characterized by recurrent episodes of peritonitis. In many cases abdominal FMF attacks can be indistinguishable from those of an acute abdominal emergency, so patients may undergo one or more laparotomies before the true nature of their disease is documented. Almost all participants (surgeons, physicians and patients) mentioned that abdominal pain in FMF patients starts in different ways. It may start suddenly from one point of the abdomen, usually from the upper part or epigastral part, and then spread out to the entire abdomen. According to several patients, in many cases it starts after joint or chest pain, nervousness, or discomfort. The patients mentioned also nausea, vomiting, sometimes high fever, constipation, diarrhea that accompany FMF abdominal attacks. Few patients mentioned headache, anxiety, nervousness, and dizziness.

“It started in the gastric part and then spread through the whole abdomen. ...The attacks started with the nausea, and after vomiting the pains become milder. Fever was very rare, I had it only one or two times during these attacks.”

Patient 1

In most cases the abdominal attacks during FMF presented several times and according to the

patients the frequency of the abdominal attacks varies from twice a week to once a week or twice a year. Usually abdominal pains during acute appendicitis occur one time. This pain does not have any periodicity. Therefore, the nature of the pain should be considered carefully in differential diagnosis. Family history of such pains should also be considered for diagnosis of FMF. Accompanying symptoms also play an important role in the diagnosis.

“.....they were once the month or twice the year, now they become more often and can be twice the week.”

Patient 5

“Every two, three months I had attacks but now the attacks become more frequent: twice or three times a week. “

Patient 7

First experience of FMF patients in medical settings and potential contributing factors to misdiagnosis

According to the study findings, due to incorrect diagnosis FMF patients undergo unnecessary surgeries. This mostly happens during their first experience with abdominal attacks and especially when they are unaware about having FMF. Majority of the FMF patients mentioned that their first attack started in childhood when they were 5-11 years old. Few of them remembered that they experienced the first attack at 20 years old or elder, and only one participant said that it started when he was 1 year old. In most cases FMF patients are diagnosed with very different diseases, including gases in abdomen, food intoxication or acute appendicitis. Most frequent symptoms that lead to unnecessary surgeries in FMF patients are severe abdominal pain with high temperature and dysfunction of the gastrointestinal tract. According to the doctors (surgeons and physicians) the very first admission of the patients with acute abdomen to the surgical department presents diagnostic difficulty especially when the patient is unaware about having FMF or if a patient is a child.

The surgeons also mentioned that they often encounter acute abdomen cases in their everyday practice. As the acute abdomen requires urgent treatment, very often surgeons do not have enough time to perform more precise diagnosis to reveal the real cause. They perform surgeries to avoid unwanted complications such as perforations or generalized peritonitis. So the surgeons in many cases prefer to operate the patients to avoid further complications than to wait. Some respondents also expressed their concern that sometimes surgeons perform surgeries for financial incentives.

“Very often the patients undergo surgeries during the first attacks, when they first time have the abdominal attacks and they are unaware about their disease.”

FGD2 P2

“Sometimes in surgical departments we have situations when we have to hurry and do not have enough time for more careful and long examinations, so we perform laparotomy. If there is laparoscope we perform laparoscopy to determine the cause of the acute abdomen.”

FGD1 P 2

However, during repeated presentation with abdominal pain, the doctors start thinking about other causes of acute abdomen including FMF and refer the patient for genetic testing.

Diagnosis of FMF abdominal pains vs. acute abdomen of other causes

In general FMF is diagnosed by clinical manifestations according to Tel-Hashomer criteria and is confirmed by the genetic testing (12;24). According to all doctors including surgeons it is very challenging to diagnose FMF acute abdominal attacks. Detailed collection of anamnesis of the disease and family history is as an integral part of the FMF differential diagnostics as mentioned by the interviewees. The physicians should collect the data about the characteristics of the patient’s abdominal pain, and assess the family history of the patient. Almost all doctors stressed the necessity of genetic testing for the confirmation of the FMF patients as it has 95% sensitivity. Moreover, several physicians stated that genetic

testing identifies the genotype and phenotype and helps predict severity of FMF and the course of the disease, such as possible development of amyloidosis. Other accompanying symptoms, such as joint and chest involvement, erysipeloid rushes, oligo- or mono-arthritis and others were also stressed by the participants that could help for the differential diagnosis. Surgeons and some physicians also mentioned laparoscopy as the appropriate differential diagnostic method. Most of doctors stressed that laparoscopy is the most preferable method to make correct diagnosis in urgent situations that is least invasive. Diagnostic laparoscopy (DL) is a minimally invasive surgery for the diagnosis of intra-abdominal diseases (56). Laparoscopy has been used by many authors for diagnosis of non-specific acute abdominal pain. The rationale for the use of DL in this setting is to prevent treatment delay that leads to poorer patient outcomes, and to avoid unnecessary laparotomy, which is associated with relatively high morbidity rates (5–22%) (56;57). Based on their work experiences many physicians stated that some laboratory indices such as ESR, amount of leukocytes, AA amyloid, C reactive protein, and also X-Ray of the chest and ultrasonography are informative for differential diagnosis. Some findings that are consistent with the diseases like appendicitis are not the same for FMF. These findings were used for development of a decision tree for differential diagnosis of FMF acute abdominal attacks and acute appendicitis.

“It is very important to consider anamnesis vitae very carefully..... I ask them (the patients) two types of questions such as whether somebody in their family has experienced acute abdominal attacks in their lifetime, and where the patient’s parents are from.

Phys. 1

“There was a huge revolution after founding genetic testing of FMF patient. It let us to diagnose even the atypical types of FMF and it can even help us find the differences between genotype and phenotype.”

Phys. 1

“.....I think that the genetic testing is more informative method. However, in 5% of patients who is clinically diseased may have not any known FMF mutations.....”

Phys. 4

“Now as we have laparoscopy it become easier to distinguish the cases where there are no serious changes in the abdomen and send the patient for the genetic testing.”

FGD 1 P2

“During FMF the white blood cell count is higher than in appendicitis, ESR also is always high, and we can see the splenomegalia during it.”

Phys. 4

One of the surgeons shared his residency experience differentiating acute abdomen of FMF from acute abdomen of other origin by measuring the temperature in different parts of the abdomen. According to the respondent, during FMF abdominal attacks the temperature is the same in every part of the abdomen but during acute appendicitis the temperature is a little bit higher in the right iliac part. This method is not supported in the literature. However, based on some studies done by Peltokallio et al thermography was used to support the true diagnosis of acute appendicitis by 63%, acute biliary tract diseases by 59% (58;59). The accuracy of thermography in breast tumors is about 75-90% in different cases (58).

“During my residency I encountered a diagnostic method for differentiation of FMF abdominal attacks from appendicitis. The doctor took the temperature from the different parts of the abdomen, during FMF all parts have the same temperature, but during inflammation of exactly one of the abdominal organs for example appendix the temperature was higher in that by 1-2 °C part than the other parts.”

FGD 1 P 4

Management of acute abdominal pains/ FMF abdominal attacks

In general when a patient admits to the emergency department due to his/her severe abdominal pain the doctors have to urgently diagnose the cause and solve it. It is believed that during acute abdominal pain especially when it is located in the right lower part in the abdomen the surgeon should not give patient analgesics as it will mask the real symptoms and may lead to development of perforation and peritonitis. But according to the literature the use of analgesics for acute abdominal pain did not cause either a delay in diagnosis or drug-related adverse effects and allow less and less patients to suffer unnecessarily while physicians conduct their clinical monitoring for acute surgical abdomen and specifically, appendicitis (60). According to our FMF patients there is no analgesic medicine that may help during abdominal pains. Even very strong analgesics could not help them with the pains and sometimes it made them even to cry as the pain is very strong. The only strategy is to wait until the pain resolves after 3-5 days. Waiting for the symptom resolution is another strategy to be considered for differentiation between FMF abdominal attacks and acute appendicitis.

“There is not any medicine that can make my pains milder during attacks and I know that I have to wait 3 days and I say to myself “wait till 3 days”.”

Patient 3

Colchicine has been the therapy of choice for FMF patients since 1972. It prevents the acute attacks of FMF and prevents the development of amyloidosis (61). Majority of participants

mentioned colchicine as the only medicine that alleviates the intensity of attacks and decreases the frequency of the abdominal attacks. Almost all doctors mentioned that it also prevents the development of amyloidosis, especially of the kidney. Besides, some of the physicians stated that the treatment with colchicine also may prevent the development of adhesions. Moreover, it can lead to the involution of already developed adhesions. Treatment with colchicine decreases also the joint and chest pains as stressed by some physicians (61).

“.....if a patient takes colchicine every day there won't be any development of adhesions and even more if the adhesions have already been developed so they will be dissolved.”

Phys. 1

“After taking colchicine everyday my attacks become milder. Now I don't have any attacks only last year I had chest pain a little but no abdominal attacks. The frequency of my attacks becomes rare.”

Patient 6

Changes in practice

Almost all study participants either doctors (physicians who deal with FMF patients and surgeries) or patients mentioned that now in Armenia, especially in Yerevan the situation regarding the management of FMF patients with abdominal attacks becomes much better than several years ago. Many of participants (patients and physicians) stated that in general nowadays most unwarranted surgeries are performed on patients who were out of Armenia, in marzes, in Russia or Europe, where doctors are not familiar with FMF. However, according to one of the physicians, 2,611 out of 14,500 FMF registered patients had undergone surgeries and most of them were appendectomies.

“10 years ago I met very often FMF patients with multiple abdominal surgeries, but now during these 5 years such misdiagnoses and incorrectly performed surgeries are rare.”

Phys. 5

Patients’ attitudes towards unnecessary surgeries

Almost all patients agreed that surgeries done during FMF attacks do not have any influence on the progress and frequency of the FMF symptoms. Although two patients mentioned that they do not consider their surgeries as unnecessary, but the rest agreed that their surgeries were performed incorrectly. Moreover, some of the patients stated that directly after their surgeries the abdominal attacks happened again. There is evidence in the literature that recurrent peritonitis during FMF leads to the development of peritoneal adhesions. It is also known that every abdominal surgery may be the reason for the development of adhesions which bring to the mechanical obstruction of bowels and may be the reason for the re-laparotomies (61). Moreover according to the literature as FMF patients have already had predisposition to the development of adhesion, fibrotic bands and mechanical constipation so surgeries on FMF patients increase the development of peritoneal adhesions and consequently bowel obstruction.

“After removal of appendix my pains hadn’t changed and I had undergone my second surgery as I had severe abdominal pain and constipation.”

Patient 3

“Very often FMF patients have undergone surgeries after appendectomy due to mechanical constipation as they develop adhesions. Moreover, FMF patients have predisposition to develop adhesions more than non FMF patients. “

FGDIP4

According to the patients, many of them have had their repeated surgeries. Based on focus group discussions we revealed that some physicians prefer to perform appendectomies in order to ensure that they do not miss possible appendicitis and further peritonitis. This notion

was also confirmed by some patients who had undergone the unnecessary surgeries. Some of the surgeons thought that it is much better to do appendectomy than to lose the patient. They also mentioned that the appendectomy was the “least of the evil”. Continuing episodes of abdominal pain cause repeated surgeries, during which the most part of the bowel or other abdominal organs will be removed.

“I think that my surgeries were not appropriate. Because it was due to my disease and there wasn’t any improvement from these surgeries.”

Patient 3

“The appendectomy is the least evil.....I knew a guy who died at 35 and only in the end the doctors understood that he had FMF and his surgeries were unwarranted, all of his organs had been removed. Every time when he had attacks they had removed appendix, gall bladder, bowels etc.”

Patient 3

We summarize the results of the focus group study in an algorithm for differential diagnosis of FMF abdominal attacks and acute appendicitis. This algorithm will allow surgeons and emergency physicians to minimize misdiagnosis of FMF patients with acute abdominal attacks. According to the algorithm when a patient seeks medical care for their acute abdominal pain, the physician should first very carefully collect the history of the disease and also ask about the family history. By asking carefully about the frequency and duration of the pains, whether they are frequent or not, or there is any medicine that alleviate the pain, how long the pains lasts, what other accompanying symptoms they have (temperature, nausea, dizziness, chest pains, arthritis) the physician can formulate a preliminary diagnosis. The family history may confirm the suspected diagnosis. After collection of anamnesis vitae and morbi the physician should perform some laboratory and diagnostic tests to finalize the diagnosis. If acute appendicitis is strongly suspected, they should remove it. However, after appendectomy the physicians should not forget about FMF and should refer the patient for genetic testing. If the results of the genetic test are consistent with FMF, colchicine treatment

should start. Even if the genetic test is negative the physician should evaluate the patient further for possible FMF as in 5% cases FMF patients might have a negative genetic test. If no serious condition (acute appendicitis) is suspected, the physician should monitor the patient. The suggested algorithm may decrease the misdiagnosis of FMF patients with acute abdominal attacks and prevent them from unnecessary surgeries.

In addition, the surgeons made other suggestions regarding genetic screening for FMF as Armenia is considered an endemic zone for the disease. They contended that it is important to implement a genetic screening of newborns for FMF. Screening will help diagnose the disease early and will allow avoiding health complications from undiagnosed FMF such as renal disorders or incorrectly performed surgeries due to FMF abdominal attacks. It is important also to increase awareness among population about FMF through mass media and internet. This information is especially needed in rural areas, in order to avoid misdiagnosis of FMF abdominal attacks. Finally, the participants suggested reducing the cost of the FMF genetic test as the only opportunity for patients to be diagnosed with FMF. Some physicians also suggested creating a centralized clinic for FMF patients' management. They mentioned that now there are departments for FMF patients in every clinic in Yerevan. These patients go to different departments and different doctors that often give them various diagnoses. It is better to concentrate diagnosis and care of FMF patients in one facility in order to reduce misdiagnosis and incorrectly performed surgeries.

Study Strengths and Limitations

This is the first study that let us assess the situation regarding surgeries in FMF patients with abdominal attacks which make the study strong. Although the study sample is small, it is derived based on the purposive sampling approach and involves physicians, surgeons and FMF patients with surgeries who have diverse but essential roles in misdiagnosis of acute abdominal pains in FMF patients with abdominal attacks in Armenia. The study instrument

was developed by the study group, it was pretested on 2 surgeons, 1 FMF patient, and 1 physician.

The study was conducted in Yerevan; and the surgeons and physicians had worked in Yerevan many years. No participants from rural areas participated. The time and budget constraints did not allow for more detailed analysis of the problem areas identified in the scope of the study.

Conclusions and Recommendations

This is a first study conducted in Armenia to assess the situation with incorrectly performed surgeries in Armenia and to identify the potential contributing factors that lead to these surgeries. Armenia is considered an endemic zone for FMF, which decrease the possibility of unnecessary surgeries, since doctors in Yerevan are more informed about the disease. However, misdiagnosis more often occurs in children and women due to difficulties with differential diagnosis. Mostly, incorrect surgeries occur in rural areas or outside of Armenia (Russia, or Europe) where the doctors are less aware about FMF disease and symptoms. We revealed that although it is difficult to differentiate acute abdominal pain in FMF from other causes of acute abdomen due to the similarity of the symptoms, the laparoscopy as well as collecting anamnesis vitae and morbi properly will help differentiating them. Further, genetic testing helps confirm FMF diagnosis.

Although the study findings revealed that now in Armenia the situation regarding FMF patients with surgeries is more satisfactory than 10 years ago, further studies are needed to better understand it. Quantitative studies among larger number of patients will help elucidate the contributing factors as well as test the algorithm. For further improvements we recommend developing guidelines and brochures about the diagnosis and differential diagnosis of FMF. It is important to distribute this information throughout of Armenia especially in areas where FMF is more common. It will be also important to conduct a similar study in rural areas and among children for more accurate assessment, especially in marzes. It

is also to increase awareness about FMF in rural areas by means of seminars and the internet. As Armenia is an endemic zone for FMF so we would also recommend screening of newborns especially in Gegarqunik, Lori and Ararat marzes. It will be very important to conduct a study for assessing the rate of acute appendicitis and among them the cases with FMF.

Reference List

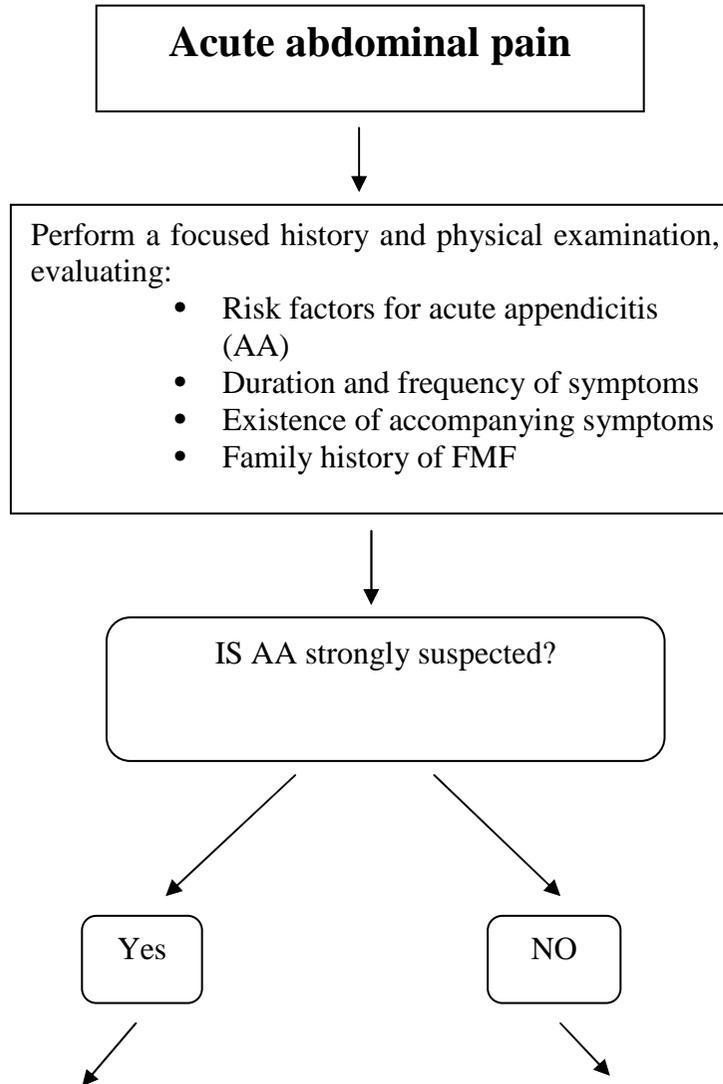
- (1) Khachadurian AK, Armenian HK. Familial paroxysmal polyserositis (familial Mediterranean fever); incidence of amyloidosis and mode of inheritance. *Birth Defects Orig Artic Ser* 1974;10(4):62-6.
- (2) Armenian HK. Genetic and environmental factors in the aetiology of familial paroxysmal polyserositis. An analysis of 150 cases from Lebanon. *Trop Geogr Med* 1982 Jun;34(2):183-7.
- (3) Sarkisian T, Ajrapetyan H, Shahsuvaryan G. Molecular study of FMF patients in Armenia. *Curr Drug Targets Inflamm Allergy* 2005 Feb;4(1):113-6.
- (4) Eliakim M. Incidence of amyloidosis in recurrent polyserositis (familial Mediterranean fever). *Isr J Med Sci* 1970 Jan;6(1):2-8.
- (5) Armenian HK, Sha'ar KH. Epidemiologic observations in familial paroxysmal polyserositis. *Epidemiol Rev* 1986;8:106-16.
- (6) Gershoni-Baruch R, Shinawi M, Leah K, Badarnah K, Brik R. Familial Mediterranean fever: prevalence, penetrance and genetic drift. *Eur J Hum Genet* 2001 Aug;9(8):634-7.
- (7) La RM, Nucera G, Diaco M, Procopio A, Gasbarrini G, Notarnicola C, et al. Familial Mediterranean fever is no longer a rare disease in Italy. *Eur J Hum Genet* 2003 Jan;11(1):50-6.
- (8) Atabek C, Temiz A, Bal k, Battal B, Delia a H, Snrer, et al. How to distinguish: appendicitis or acute abdominal attack of FMF? 2007.
- (9) Schwabe AD, Peters RS. Familial Mediterranean Fever in Armenians. Analysis of 100 cases. *Medicine (Baltimore)* 1974 Nov;53(6):453-62.
- (10) Meyerhoff JO. eMedicine Specialties> Rheumatology> Infectious Arthritis.
- (11) Sevoyan M. Evaluation of the effectiveness of colchicine therapy in preventing renal amyloidosis in patients with Familial Mediterranean Fever in Yerevan, Armenia. 2005.
- (12) Livneh A, Langevitz P. Diagnostic and treatment concerns in familial Mediterranean fever. *Baillieres Best Pract Res Clin Rheumatol* 2000 Sep;14(3):477-98.
- (13) Ozel AM, Demirturk L, Yazgan Y, Avsar K, Gunay A, Gurbuz AK, et al. Familial Mediterranean fever. A review of the disease and clinical and laboratory findings in 105 patients. *Dig Liver Dis* 2000 Aug;32(6):504-9.
- (14) Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med* 1967 Aug;43(2):227-53.
- (15) Lidar M, Livneh A. Familial Mediterranean fever: clinical, molecular and management advancements. *Neth J Med* 2007 Oct;65(9):318-24.
- (16) Onen F. Familial mediterranean fever. *Rheumatology international* 2006;26(6):489-96.

- (17) Radisic M, Santamarina J, Froment R. Sustained, progressive, nonresolving abdominal pain: a previously undescribed clinical presentation of familial Mediterranean fever. *Clin Rheumatol* 2006 Nov;25(6):914-6.
- (18) Ben-Chetrit E, Levy M. Familial mediterranean fever. *The Lancet* 1998;351(9103):659-64.
- (19) Simon A, van der Meer JW, Drenth JP. Familial Mediterranean fever--a not so unusual cause of abdominal pain. *Best Pract Res Clin Gastroenterol* 2005 Apr;19(2):199-213.
- (20) Livneh A, Langevitz P, Zemer D, Padeh S, Migdal A, Sohar E, et al. The changing face of familial Mediterranean fever. *Semin Arthritis Rheum* 1996 Dec;26(3):612-27.
- (21) Livneh A. Familial mediterranean fever: a continuously challenging disease. *Isr Med Assoc J* 2011 Apr;13(4):197-8.
- (22) Sarkisian T, Ajrapetian H, Beglarian A, Shahsuvarian G, Egiazarian A. Familial Mediterranean Fever in Armenian population. *Georgian Med News* 2008 Mar;(156):105-11.
- (23) Ben-Chetrit E, Touitou I. Familial mediterranean Fever in the world. *Arthritis Rheum* 2009 Oct 15;61(10):1447-53.
- (24) Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997 Oct;40(10):1879-85.
- (25) Pras M. Familial Mediterranean fever: from the clinical syndrome to the cloning of the pyrin gene. *Scand J Rheumatol* 1998;27(2):92-7.
- (26) Lidar M, Tokov I, Chetrit A, Zaks N, Langevitz P, Livneh A. Diagnosis delay in familial Mediterranean fever (FMF): social and gender gaps disclosed. *Clin Exp Rheumatol* 2005 May;23(3):357-63.
- (27) Stoffman N, Magal N, Shohat T, Lotan R, Koman S, Oron A, et al. Higher than expected carrier rates for familial Mediterranean fever in various Jewish ethnic groups. *Eur J Hum Genet* 2000 Apr;8(4):307-10.
- (28) Navarro FJA, Tβrraga LPJ, RodrØiguez MJA, L≤pez CMA. Validity of tests performed to diagnose acute abdominal pain in patients admitted at an emergency department. *Revista espa±ola de enfermedades digestivas: organo oficial de la Sociedad Espa±ola de PatologØa Digestiva* 2009;101(9):610.
- (29) Eldar S, Nash E, Sabo E, Matter I, Kunin J, Mogilner JG, et al. Delay of surgery in acute appendicitis**. *The American journal of surgery* 1997;173(3):194-8.
- (30) Graff L, Russell J, Seashore J, Tate J, Elwell A, Prete M, et al. False negative and False positive Errors in Abdominal Pain Evaluation Failure to Diagnose Acute Appendicitis and Unnecessary Surgery. *Academic Emergency Medicine* 2000;7(11):1244-55.
- (31) Kaya B, Eri+f C, U+°tum Y. Delay in Diagnosis of Intestinal Obstruction in a Patient with Familial Mediterranean Fever. *Clinical Medicine*2010.

- (32) Mellinkoff SM. The differential diagnosis of abdominal pain. 1 ed. Blakiston Division; 1959.
- (33) Irvin TT. Abdominal pain: a surgical audit of 1190 emergency admissions. *Br J Surg* 1989 Nov;76(11):1121-5.
- (34) Sherman R. Abdominal Pain. 1990.
- (35) Marincek B. Nontraumatic abdominal emergencies: acute abdominal pain: diagnostic strategies. *Eur Radiol* 2002 Sep;12(9):2136-50.
- (36) Prystowsky JB, Pugh CM, Nagle AP. Current problems in surgery. Appendicitis. *Current problems in surgery* 2005;42(10):688.
- (37) Akar S, Soyuturk M, Onen F, Tunca M. The relations between attacks and menstrual periods and pregnancies of familial Mediterranean fever patients. *Rheumatology international* 2006;26(7):676-9.
- (38) Kisacik B, Kalyoncu U, Erol MF, Karadag O, Yildiz M, Akdogan A, et al. Accurate diagnosis of acute abdomen in FMF and acute appendicitis patients: how can we use procalcitonin? *Clin Rheumatol* 2007 Dec;26(12):2059-62.
- (39) Zissin R, Rathaus V, Gayer G, Shapiro-Feinberg M, Hertz M. CT findings in patients with familial Mediterranean fever during an acute abdominal attack. *Br J Radiol* 2003 Jan;76(901):22-5.
- (40) Stone R. Primary care diagnosis of acute abdominal pain. *Nurse Pract* 1996 Dec;21(12 Pt 1):19-30, 35.
- (41) Wikstrom M, Wolf A, Birk D, Brambs HJ. Abdominal CT in familial Mediterranean fever: a case report. *Abdom Imaging* 1998 Mar;23(2):147-9.
- (42) Reissman P, Durst AL, Rivkind A, Szold A, Ben-Chetrit E. Elective laparoscopic appendectomy in patients with familial Mediterranean fever. *World J Surg* 1994 Jan;18(1):139-41.
- (43) Zemer D, Revach M, Pras M, Modan B, Schor S, Sohar E, et al. A controlled trial of colchicine in preventing attacks of familial mediterranean fever. *N Engl J Med* 1974 Oct 31;291(18):932-4.
- (44) Hernandez JA, Swischuk LE, Angel CA, Chung D, Chandler R, Lee S. Imaging of acute appendicitis: US as the primary imaging modality. *Pediatr Radiol* 2005 Apr;35(4):392-5.
- (45) Old JL, Dusing RW, Yap W, Dirks J. Imaging for suspected appendicitis. *Am Fam Physician* 2005 Jan 1;71(1):71-8.
- (46) Ang A, Chong NK, Daneman A. Pediatric appendicitis in "real-time": the value of sonography in diagnosis and treatment. *Pediatr Emerg Care* 2001 Oct;17(5):334-40.
- (47) Hastings RS, Powers RD. Abdominal pain in the ED: a 35 year retrospective. *Am J Emerg Med* 2011 Sep;29(7):711-6.

- (48) Graff IV, Louis G, Robinson D. Abdominal pain and emergency department evaluation. *Emergency medicine clinics of North America* 2001;19(1):123-36.
- (49) Graff L, Radford MJ, Werne C. Probability of appendicitis before and after observation. *Annals of emergency medicine* 1991;20(5):503-7.
- (50) McCaig LF, Burt CW. National hospital ambulatory medical care survey: 2002 emergency department summary. Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2004.
- (51) Durai R, Khan A, Siddiqui M, Oke T. Positive Murphy's sign in acute appendicitis. *Br J Hosp Med (Lond)* 2011 Jul;72(7):413-Unknown.
- (52) ADDISS DG, SHAFFER N, FOWLER BS, TAUXE RV. The epidemiology of appendicitis and appendectomy in the United States. *American journal of epidemiology* 1990;132(5):910.
- (53) Blewett CJ, Krummel TM. Perforated appendicitis: past and future controversies. 1995 p. 234.
- (54) Kasifoglu T, Cansu DU, Korkmaz C. Frequency of abdominal surgery in patients with familial Mediterranean fever. *Intern Med* 2009;48(7):523-6.
- (55) Celebi S, Acik Y, Deveci SE, Bahcecioglu IH, Ayar A, Demir A, et al. Epidemiological features of irritable bowel syndrome in a Turkish urban society. *J Gastroenterol Hepatol* 2004 Jul;19(7):738-43.
- (56) Stefanidis D, Richardson WS, Chang L, Earle DB, Fanelli RD. The role of diagnostic laparoscopy for acute abdominal conditions: an evidence-based review. *Surg Endosc* 2009 Jan;23(1):16-23.
- (57) Paterson-Brown S, Eckersley JR, Sim AJ, Dudley HA. Laparoscopy as an adjunct to decision making in the 'acute abdomen'. *Br J Surg* 1986 Dec;73(12):1022-4.
- (58) Emery M, Jones J, Brown M. Clinical application of infrared thermography in the diagnosis of appendicitis. *Am J Emerg Med* 1994 Jan;12(1):48-50.
- (59) Peltokallio P, Svinhufvud U, Rantakaulio M, Varjoranta K. The significance of thermography in the diagnosis of acute abdominal disease. *Am J Roentgenol Radium Ther Nucl Med* 1975 Sep;125(1):164-71.
- (60) Vermeulen B, Morabia A, Unger PF, Goehring C, Grangier C, Skljarov I, et al. Acute appendicitis: influence of early pain relief on the accuracy of clinical and US findings in the decision to operate—a randomized trial. *Radiology* 1999;210(3):639.
- (61) Berkun Y, Ben-Chetrit E, Klar A, Ben-Chetrit E. Peritoneal adhesions and intestinal obstructions in patients with familial Mediterranean fever—are they more frequent?: Elsevier; 2007 p. 316-21.

An algorithm for differential diagnosis of FMF abdominal pains and acute appendicitis



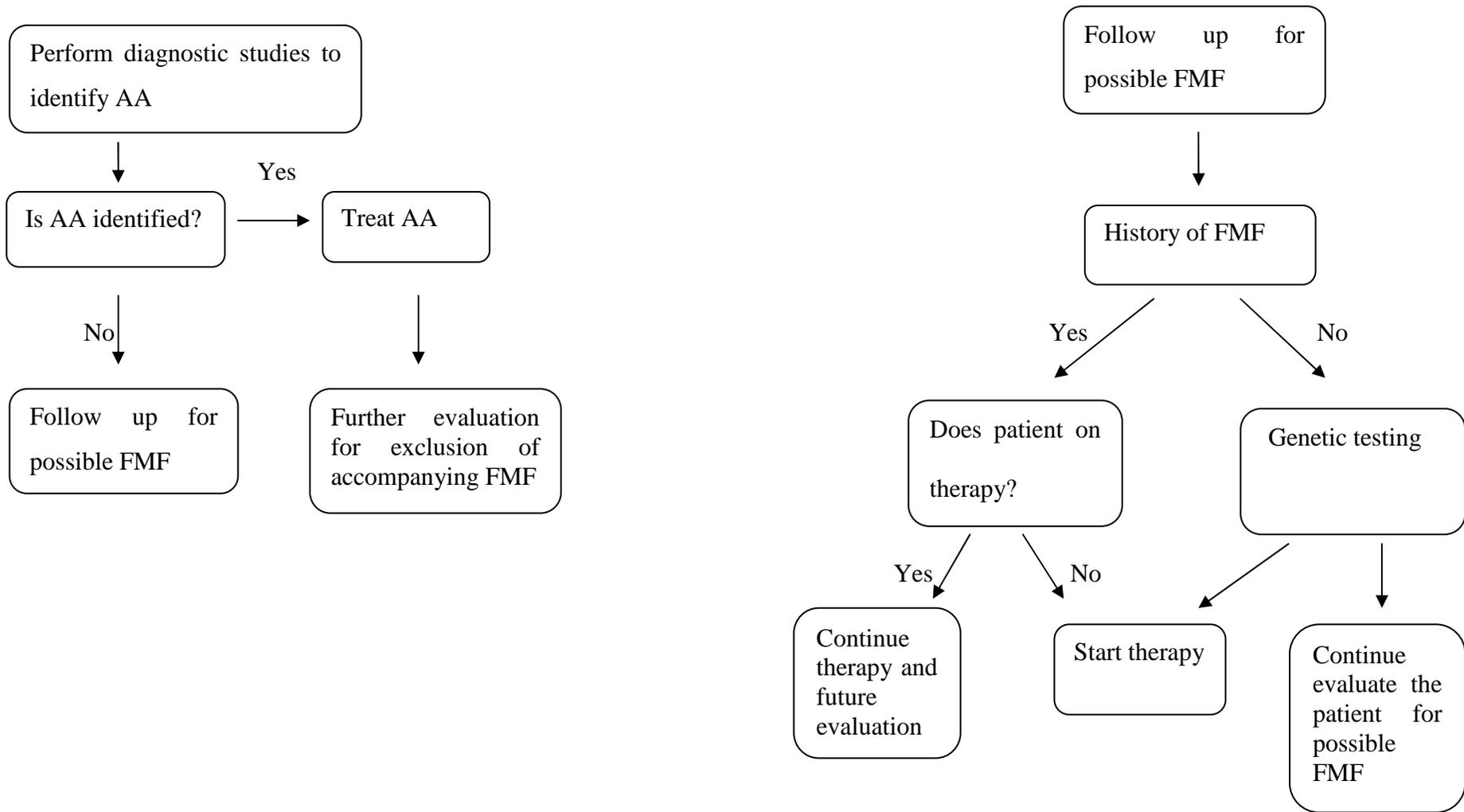


Figure1

Appendix 1

American University of Armenia Institutional Review Board # 1/Committee on Human Research College of Health Sciences Subcommittee for Student Theses

CONSENT FORM

(For FMF patients)

Assessment of the problem and the main determinants of incorrectly performed laparotomies in FMF patients with abdominal attacks in Yerevan, Armenia A qualitative study

Hello, my name is Kristina Mnatsakanyan. I am a physician and a graduate student in the College of Health Sciences at the American University in Armenia. The College of Health Sciences of AUA is conducting a study to investigate FMF acute abdominal attack differences from an acute abdomen of other etiology.

You are being asked to participate in this study as a person who has experienced FMF abdominal attacks and has undergone surgery. We would like to talk to you about your surgery, the reasons and consequences of that surgery.

We are interested in your opinions and suggestions. Participation involves only one individual interview with you, depending on your availability and willingness to participate in the interview. The interview will last for about one hour. We will take notes and if you permit we would like to audio record the interview to make sure that no idea remains out of our attention.

There is no direct benefit and risk for participating in this study beyond contributing to understanding the situation regarding incorrectly performed laparotomies for acute abdomen among FMF patients with abdominal attacks in Yerevan, Armenia. Your participation is confidential as your name and telephone number will be used only by me. Your name and

any characteristics that identify you will not be associated with your interview or with the results of this study. Brief quotes not attributable to you may be used in the results of this study. Your name will not appear in reports and presentations. Only aggregated data will be presented in the final report.

You are free to decline participation at any time even after we start the interview. Your participation in this study is voluntary and you are free to refuse participation without negative consequences for you or the treatment you receive. You may withdraw from the study at any time and any data collected from you will be destroyed should you withdraw after the interview.

If you have any questions about this study you can contact Dr. Varduhi Petrosyan, the Associate Dean of the College of Health Sciences at AUA calling 512592. If you feel you have not been treated fairly or think you have been hurt by joining this study, please contact Dr. Hripsime Martirosyan, AUA Human Subjects Administrator at (374 1) 51 25 61. If you consent to participate, we can start.

American University of Armenia
Institutional Review Board # 1/Committee on Human Research
College of Health Sciences Subcommittee for Student Theses
CONSENT FORM

(For physicians/surgeons)

Assessment of the problem and the main determinants of incorrectly performed laparotomies in FMF patients with abdominal attacks in Yerevan, Armenia A qualitative study

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The purpose of this study is to understand the situation related to FMF patients in Armenia, particularly those who undergo surgery. You are being asked to participate in this study as you are a physician/surgeon and have an experience working with FMF patients who had acute abdomen. We are interested in your opinions and suggestions. Participation involves only one interview/discussion with you, depending on your availability and willingness to participate in the interview. Interview/discussion will last for about one hour. We will take notes and if you permit we will audio record the interview/discussion to make sure that no idea remains out of our attention.

There is no personal risk or benefit for participating in this study beyond contributing to understanding the situation regarding incorrectly performed laparotomies for acute abdomen among FMF patients with abdominal attacks in Yerevan, Armenia.

Your participation is confidential and anonymous. Your name and any characteristics that identify you will not be associated with your interview or with the results of this study. Brief

quotes not attributable to you may be used in the results of this study. Your name and position will not appear in reports and presentations. All your comments will be used for research purpose only and the aggregated data will be presented in the final report.

You are free to decline participation at any time even after interview or skip any question you are not willing to answer. Your participation in this study is voluntary and you are free to refuse participation without consequences. You may withdraw from the study at any time and any data collected from you will be destroyed should you withdraw after interview.

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Appendix 2

In-Depth Interview Guide for FMF patients

Date _____

Time _____

Interviewer name _____

The purpose of our discussion today is to learn about your experience as a FMF. I will ask you question about your FMF symptoms, when and how you first applied for the health care, and how the disease, the diagnosis and the treatment affected your life. If you are ready, let's proceed".

1. How far back can you remember about your first attack? Could you please describe your abdominal pain?

Probes: When did you first time experience an abdominal attack? How old were you at that time? How often were your abdominal attacks? How did they start? Was there any connection between the seasons? Please mention what other symptoms did you have during the abdominal pains? How are your attacks now?

2. Next, I would like to ask you to describe your experience with medical providers and health care system. Could you, please, remember when you first saw a physician in relation to your abdominal attacks and how and when you received a diagnosis of FMF?

Probes: When and where did you first apply to the HCP for your abdominal pains??

What specialist did you see? Do you remember the reason for which you went to see HCP? What was your diagnosis when you first time saw the doctor? What was your

diagnosis for which you had a surgery? What kind of surgery have you undergone?

Was the diagnosis confirmed after the surgery?

3. What were the results after surgery? Has the nature of your abdominal attacks changed after the surgery? Did you have other surgeries? When? What was the diagnosis?
4. Who referred you to the genetic center and when? Have you had a genetic test? When? Where? Do you receive any treatment? What was the result under the treatment by colchicine?
5. In your opinion was the surgery needed or not? What could have been done to escape the [unnecessary] surgery?
6. Are there other things that we did not discuss but you feel are important to talk about?

Thank you for participating in our study

Focus group interview guide for surgeons

Place _____

Date _____

Time _____

Moderator _____

Recorder _____

In your everyday work, you have to deal with abdominal pain and acute abdomen. However, many nosologies present with acute abdomen. Let us discuss your experience with acute abdomen and differential diagnosis of patients with acute abdomen, especially in relation to the periodic disease or FMF.

1. First, could you, please, discuss how often you see patients with acute abdomen and what are the most common characteristics of this phenomenon in the patient population?
Probes: What kind of symptoms do the patients mention? Are there any other symptoms that the patients could have during an acute abdomen besides abdominal pain? From your work experience what situations most frequently lead to development of an acute abdomen?
2. What are the main diagnostic steps in patients with acute abdomen that you perform?
How often in your practice do you consider the diagnosis of FMF when a patient presents with signs of acute abdomen? What particular diagnostic tests should be performed to identify FMF abdominal attacks?
3. From your experience, how often you or your colleagues perform surgeries on patients who have undiagnosed FMF and what are the potential consequences for the patients, providers, and the health care system?
What are your steps when the cause of an acute abdomen isn't identified by the mentioned diagnostic mechanisms?
4. Are you satisfied with the current state of differential diagnosis of FMF abdominal attacks? How in your opinion, this process can be improved? Do you believe that misdiagnosis can be avoided due to improving diagnosis of FMF abdominal attacks?
Are there other things that we did not discuss but you feel are important to talk about?

Thank you for participating in our study

In-depth interview guide for Physicians (who deal with the FMF patient's care)

We would like to ask several questions regarding diagnosis and treatment of FMF abdominal attacks and acute abdomen of other causes as you daily meet many patients with FMF.

1. Do you believe that there is a diagnostic challenge for the health care providers in Armenia concerning FMF abdominal attacks? In your practice how often do you see FMF patients that have undergone surgery due to acute abdominal attacks?
2. What should be done to avoid surgery on these FMF patients? In what diagnostic step was made a mistake that the FMF abdominal attack led to the surgery? Is there any diagnostic method that can correctly find FMF?
3. What kind of diagnostic tests are performed and should be performed to identify FMF abdominal attacks in Armenia? What is the diagnostic method that is the most informative?
4. What situations of acute abdominal attacks usually lead to a rapid surgery in Armenia? What kind of mistakes can be made? What kind of consequences leads to these mistakes? What cases of FMF do need quick surgery?
5. Do you have any suggestions about the correct diagnosis of FMF abdominal pains which will let doctors to escape surgeries?

Are there other things that we did not discuss but you feel are important to talk about?

Thank you for participating in our study