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CLINICAL AND GENETIC CHARACTERISTICS OF THE ABDOMINAL AND DIGESTIVE SYSTEM MANIFESTATIONS IN ARMENIAN CHILDREN WITH FAMILIAL MEDITERRANEAN FEVER

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Abstract

Familial Mediterranean fever (FMF) is an autosomal recessive inherited disease affecting mainly certain ethnic groups of Mediterranean origin and characterized by febrile aseptic polyserosites. FMF as an ethnic disorder is widespread in Armenia and it is more often diagnosed in children recently. Genetic testing of FMF is efficient for diagnosis of the disease and allows to diagnose atypical cases. MEditerranean FeVer (MEFV) gene frequency and the prevalence of heterozygous carriers of one of MEFV mutation in Armenian population are rather high: 0.21 (1:5). The total number of FMF children in the National Pediatric Centre for FMF (NPC for FMF) increased from 500 to 1900 since 2003 and the annual number of newly diagnosed pediatric cases during the last 5 years reached 300-350. Different abdominal or digestive system manifestations are observed in FMF. They make the differential diagnosis difficult and may result in late diagnosis of FMF and complicated course.

The aim is to investigate clinical and genetic characteristics of the abdominal and digestive system manifestations in Armenian children with FMF.

During 1997-2008 we observed 715 patients with FMF at the NPC for FMF. There were 438 boys and 277 girls aged from 3 months to 17 years (mean age: 8.64±0.17). The diagnosis of FMF and severity of disease were confirmed according to the generally recognized criteria [Livneh A. et al., 1997; Livneh A., Langevitz P., 2000] and MEFV mutation analysis.

Besides FMF abdominal febrile attacks (92.4%) associated with homozygotes for M694V and compound-heterozygotes for three main mutations M694V, M680I, V726A ($p<0.05$), a number of other abdominal and digestive system manifestations of FMF have been observed: adhesive intestinal obstruction (AIO) (3.2%), hepatomegaly (17.7%), splenomegaly (9.9%), concominant ulcerative colitis (UC) (0.4%), as well as protracted febrile myalgia (PFM) (2.7%), Henoch-Shonlein purpura (HSP) (1.5%), Behcet disease (BD) (0.1%). Some of these diseases and symptoms were more frequent than expected. The frequency of AIO, FMF-associated vascuitides, UC was associated with M694V mutation, mainly, homozygous genotype, high disease severity, early onset and delayed diagnosis. Patients with UC had atypical onset of disease during the first year of life: recurrent febrile colics, diarrhea and/or abacterial haemocolitis. Later myalgia, arthritis, polyserosites and resistance to treatment of UC were observed.

Thus, FMF patients with severe course of disease and M694V mutation, especially with homozygous genotype were at a high risk for abdominal and digestive system manifestations. Some of them (AIO, UC, splenomegaly) might be considered as possible markers of severe course, even in the absence of typical FMF symptoms. They might be the early, first and only manifestations of FMF.

Considering the high prevalence of FMF in Armenia, we believe that the genetic screening for FMF might be indicated for children with some abdominal and gastrointestinal manifestations: adhesive (mechanical) intestinal obstruction, FMF associated vasculitis (HSP, PFM, BD), inflammatory bowel disease (UC, Crohn's disease), splenomegaly of an unknown origin, recurrent abdominal pains, especially in case of early disease onset, atypical presentations and resistance to treatment. Early diagnosis and treatment of FMF digestive system manifestations improve the course of disease and prevent amyloidosis.

Keywords: *Familial Mediterranean fever, children, abdominal and digestive system manifestations, clinical and genetic characteristics.*

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INTRODUCTION

The Familial Mediterranean fever (FMF; OMIM 249100 "Online Catalogue of Mendelian Inheritance in Man") is the most common autoinflammatory syndrome in the group of Hereditary Periodic Fever Syndromes (HPFSs) characterized by seemingly unprovoked inflammation in the absence of autoimmune or infective causes [*Lidar M., Livneh A., 2007*]. FMF is transmitted in an autosomal recessive form of inheritance and affects mainly Sephardic Jews, Arabs, Armenians, Turks and other ethnic groups of Mediterranean origin. This syndrome is characterized by recurrent, self-limited attacks of fever and aseptic serosal inflammation (peritonitis, pleuritis, synovitis) [*Padeh S., 2005; Stojanov S., Kastner D., 2005; Rigante D. et al., 2006*]. FMF is quite frequent in non-Mediterranean basin countries due to active migration, increased number of mixed marriages, and other factors [*Mor A. et al., 2003; Yepiskoposyan L., Harutyunyan A., 2007*].

As an ethnic disease FMF is widespread in Armenia. Since 1997 nearly 12,000 patients have been examined in the Centre of Medical Genetics (CMG) of the Republic of Armenia (RA) and *MEditerranean FeVer* gene (MEFV) mutations and genotypes, as well as phenotype-genotype correlations confirmed. MEFV gene frequency and the prevalence of heterozygous carriers of one of *MEFV* mutation in Armenian population are rather high: 0.21 (1:5) [*Torossyan Y. et al.,* 2000; *Hayrapetyan A., 2002; Sarkissian T. et al., 2005; 2007*]. Since 2003 until now, the total number of FMF children in NPC for FMF increased from 500 to 1900. During the last 5 years the annual number of newly diagnosed FMF pediatric cases reached 300-350 due to early diagnosis and timely referrals. The number of children with FMF, especially those with early manifestations, has increased nearly twice in some regions during the last 10 years [*Amaryan G. et al., 2005; Astvatsatryan V. et al., 2005*]. These data indicate the significance of FMF problem in Armenia.

It is well known that in addition to the acute abdominal attacks other different abdominal or digestive system manifestations of FMF could be observed to make the differential diagnosis difficult [*Astvatzatryan V. et al., 1994; Mor A. et al., 2003; Lidar M., Livneh A., 2007*]. A. Mor and co-authors suggested to classify these manifestations as four groups: FMF attack-related manifestations; manifestations unrelated to FMF attacks; adverse effects of colchicine treatment; reactive amyloidosis-related FMF manifestations [*Mor A. et al., 2003*]. Several studies reported that more than 50% FMF patients are seen by gastroenterologists and undergo different abdominal examinations (imaging, endoscopy with biopsy, etc.) before the final diagnosis is made. Many doctors in different countries are not well aware of FMF manifestations and treatment of this disease. This results in late diagnosis of FMF and increases the prevalence of complicated cases of the disease [*Mor A. et al., 2003*].

Therefore, the aim of this study is to investigate clinical and genetic characteristics of the abdominal and digestive system manifestations in Armenian children with FMF.

MATERIAL AND METHODS

During 1997-2008 we observed 715 patients (438 boys and 277 girls) with FMF at the NPC for FMF. The age ranged from 3 months to 17 years (mean age: 8.64±0.17).

The diagnosis of FMF was confirmed and disease severity determined according to generally recognized criteria [*Livneh A. et al., 1997*]. Moderate (82.6%) and severe (8.5%) course of FMF was observed in majority of patients. For the final FMF diagnosis children with FMF attacks were hospitalized at the General Pediatrics Department of the "Arabkir" Medical Center. There were referrals from the polyclinics (primary health-care clinics) by family physicians and pediatricians or emergency reception to the hospital. Follow-up was managed at the NPC for FMF.

The genetic analysis was performed in the Centre of Medical Genetics (CMG) of the Republic of Armenia. For FMF genetic testing the isolated DNA has been amplified using PCR. Restriction analysis of PCR products from genomic DNA was used to identify MEFV gene mutations. The digested products were separated by electrophoresis on 2% agarose gels. At present at the CMG twelve MEFV mutations are investigated and 23 different genotypes identified [*Hayrapetyan A., 2002;*

Sarkissian T. et al., 2007]. In this study we groupped them into 5 relatively homogeneous subgroups according to the presence of "severe" M694V mutation:

- *homozygotes* (237 patients) - M694V/M694V (211), M680I/M680I (16), V726A/V726A (8);
- *M694V heterozygotes*: M694V/0 *(61 patients);*
- *M694V compound-heterozygotes:* M694V/other (*257 patients);*
- O*ther compound-heterozygotes:* other/other (*93 patients);*
- O*ther heterozygotes*: other/0 (*39 patients).*

The statistical analysis was performed on a Pentium-4 personal computer using a standard package of Epi-Info 2000 program. For comparison of two nominal variables in table two by two Yet's corrected chi-square test for continuity was used.

RESULTS AND DISCUSSION

1. FMF attack-related abdominal and digestive system manifestations

There are two types of peritoneal involvements in FMF. The most common form is characterized by recurrent, self-limited *abdominal attacks* with a clinical outline simulating an "acute abdomen" and sometimes leads to unnecessary abdominal surgeries [*Tireli G. et al., 2006*]. Typical abdominal pain attacks are characterized by sudden onset of fever and generalized, diffuse abdominal pain, guarding of the abdominal muscles, rebound tenderness, and abdominal distention, mimicking acute appendicitis, the attack is usually self-limited, short-term and lasts 24-72 hours. The medical histories of patients often include appendectomy (9-10%), explorative laparotomy or laparoscopy, but only in 5% of cases there was acute appendicitis with small amounts of sterile inflamed peritoneal fluid containing fibrin and polymorphonuclear cells, as a peritoneal reaction to repetitive inflammation Ascites with large amount of peritoneal fluid are uncommon manifestations of FMF; and impaired liver function, portal hypertension or nephrotic syndrome should be usually excluded in such cases [*Majeed H. et al., 1999; Mor A. et al., 2003; Padeh S., 2005; Rigante D. et al., 2006*].

Abdominal attacks (recurrent aseptic peritonitis) as a typical clinical feature of FMF were observed in 661 (92.45%) patients. Such episodes were indicated as the first symptom by 372 (56.3%) children. The incidence of abdominal crises depended on the type of *MEFV* mutation ranging at various genotypes (89.7% - 94.5%). The highest level of abdominal attacks was in homozygotes (96.7%), mainly for *M694V* (84.5%) *(χ^2=20.32; p<0.05)***.** The prevalence of abdominal attacks was also observed at the following compound-heterozygous genotypes: M694V/M680I (92%), M694V/V726A (90%), V726A /M6801 (92.8%).

The risk of abdominal attacks in M694V-homozygotes and compound-heterozygotes (M694V/M694V; M694V/others) was, correspondingly, 3.4-fold (Odd's Ratio (OR): 3.35; 95% Confidence Interval (CI): 1.2 ÷ 8.72; Exact Fisher's Test (F): <0.05) and 2.5-fold higher in comparison with heterozygotes for *M694V* (OR: 2.46; CI: 1.00 ÷ 5.98; Yet's corrected chi-square test (c^2) =3.79; p<0.05) (Figure 1). Thus, the frequency of abdominal attacks in FMF patients was associated with the genotype and was higher in *M694V* homozygotes and compound-heterozygotes for three main mutations (*M694V/V726A*, M694V/*M680I,* V726A/M680I).

The adhesive (mechanical) intestinal obstruction is another type of peritoneal involvements in FMF, which develops due to peritoneal adhesions; apart amyloidosis, adhesive intestinal ob-

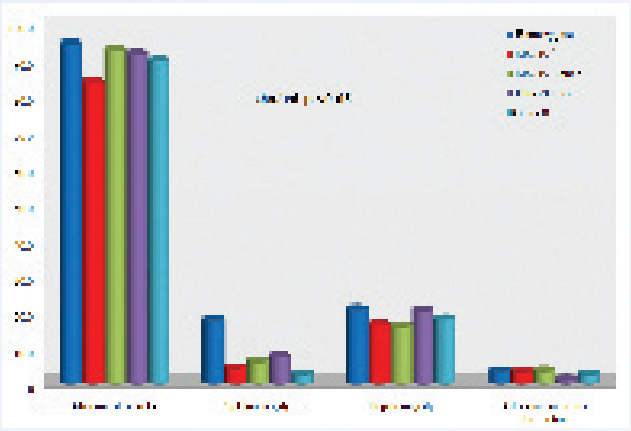

Figure 1. *The risk of abdominal attacks, splenomegaly, hepatomegaly and adhesive intestinal obstruction and genotypes in children with FMF (shaded p <0.05).*

struction (AIO) is a second typical life-threatening complication of FMF [*Ciftci A. et al., 1995; Tireli G. et al., 2006; Berkun Y. et al., 2007*]. Obstructing intestinal adhesions are more typical for severe course of the disease and associated with recurrent aseptic peritonitis. The sterile exudates in the peritoneal cavity contain fibrin and polymorph nuclear cells and result in primary peritoneal adhesions [*Ciftci A. et al., 1995; Tireli G. et al., 2006*]. Spontaneous AIO may occur despite the colchicine treatment [*Ciftci A. et al., 1995; Berkun Y. et al., 2007*]. As an additional factor for AIO complication in FMF the overactivity of anti-inflammatory cytokines was supposed [*Berkun Y. et al., 2007*]. It is still under discussion whether AIO is a primary complication of recurrent peritonitis in case of FMF or it is secondary to a previous insult to the inflamed peritoneum during abdominal surgery. Anyway, it is especially important to diagnose this severe complication in time to diminish the risk of intestinal strangulation and necrosis [*Berkun Y. et al., 2007*].

AIO was observed in 23 (3.2%) FMF patients. Sixteen children had an early disease onset during the first three years of life, which did not significantly influence the development of AIO (Relative Risk (RR) =1.17 (0.44÷3.16); c^2=0.01; p=0.95). At the same time, FMF was diagnosed rather late (7.09±0.74 years) in comparison with all the observed (715) FMF patients (5.25±0.15 years; t=2.207; p=0.03). Correspondingly, the colchicine therapy in this group was initiated later (on average after 7.3 years of the disease onset), which may also contribute to the complicated course of FMF. In 19 of 23 FMF patients with AIO we revealed the prevalence of M694V mutation in various genotypes and 1/3 of them were homozygous. The frequency of AIO was 1.5-3.5 times higher in *M694V* carriers, but the risk of AIO did not depend on MEFV genotype (c^2 =1.94; p=0.75*)* (Figure 1). Twenty of 23 patients with AIO developed a severe and moderate (bordering to severe) course of FMF. The statistically significant association between AIO and the disease severity in primary admitted and untreated FMF patients was revealed *(*c^2=6.65; p<0.04). Thus, M694V mutation carriers with a severe course of disease, especially homozygotes were at higher risk of AIO development. These data coincide with several reports [*Tireli G. et al., 2006; Berkun Y. et al., 2007*]. We suppose to investigate Armenian patients with AIO for FMF and MEFV gene mutations. As identification of the MEFV gene mutation spectrum has an important prognostic and diagnostic value, it might help to diminish the risk of AIO.

FMF patients experience different *dyspeptic symptoms***,** including constipation during abdominal attacks [*Ayvazyan A., 1982; Astvatsatryan V., Torosyan Y., 1989; Mor A. et al., 2003; Mirzabekyan K. et al., 2005*]. In 15-20% of them diarrhea or vomiting accompanied the abdominal pains. *Dyspeptic symptoms* were observed in 194 (27.1%) FMF patients. In 73 (10.2%) children the abdominal attacks were accompanied with diarrhea or constipation, especially at early onset of FMF. Patients of older ages, 121 (16.9%), developed nausea and vomiting during attacks, as well as recurrent abdominal pains in attack-free periods. Nausea and vomiting were significantly often observed in patients with M694V mutation (OR: 1.89; CI: 1.1 ÷ 3.29; F = 0.02) compared to patients with other mutations. Considering the high prevalence of FMF in Armenia, the genetic screening for FMF might be indicated for children with recurrent abdominal pains.

2. FMF abdominal manifestations unrelated to the attacks

Besides the typical peritoneal attacks, FMF course might be complicated by gastrointestinal (GI) disorders secondary to FMF: gastroduodenitis (GD), gastroesofageal reflux (GER), biliary dyskinesia, etc., especially in long-term cases. Particularly, the abdominal pains in attack-free period were observed in 5% of cases [*Livneh A. et al., 1996*]. These disorders could be asymptomatic and diagnosed only after special investigations (endoscopy, ultrasound, etc.) [*Astvatsatryan V. et al., 1994; Mor A. et al., 2003*]. *Helicobacter pylori* infection is another well-known and common cause of recurrent abdominal pains [*Demirturk L. et al., 2005; Mirzabekyan K. et al., 2005*]. Some authors suggested that GI disorders result from microcirculatory changes due to frequent FMF attacks. The systemic amyloidosis of vessels may also contrib-

ute to organs/tissues ischemia, ulcerations and sometimes vasculitis [*Ter-Kasparova M., 2002*].

Mild *splelnomegaly* (up to 3-5 *cm* under left costal margin) with incidence of 10-30 % was found in children with FMF [*Ayvazyan A., 1982; Astvatsatryan V., Torosyan Y., 1989; Kashmir T. et al., 1993).* The significant splenomegaly is usually observed during attacks of FMF. It results from pulp hyperplasia of the spleen and severe blood congestion, as well as due to accumulation of amyloid deposits in case of systemic amyloidosis [*Ter-Kasparova M., 2002*]. It is typical for severe course of FMF with some MEFV gene mutations [*Kashmir T. et al., 1993; Mor A. et al., 2003*].

The splenomegaly was observed in 71 (9.9 %) of FMF patients during both periods of disease. In 24 patients it was more than 2 *cm* (up to 5 *cm* under costal margin). The risk of splenomegaly depended on the type of MEFV gene mutation (c^2=24.86; p<0.0001) and was higher in M694V mutation carriers. The risk of splenomegaly was 3.3 times higher (OR: 3.37; 95% Cl 1.46÷8.07; F = 9.04; p<0.05) in homozygotes for *M694V* (M694V/M694V) (Figure 1). In case of marked spleen enlargement (>2 *cm*), it increased 4.2 times (OR: 4.20; 95% CI: 1.70÷10.58; F =11.37; p<0.05) compared to compound-heterozygotes and heterozygotes without M694V mutation. The splenomegaly was associated with severity of FMF (c^2=22.15; p<0.0001) and its risk was 4.3 times higher in case of severe course of disease compared to those with the mild one (OR: 4.33; 2.21÷8.41; p<0.0001). However, there was no difference between the degree of the spleen enlargement (<2> *cm*) and the disease severity.

Thus, the risk of splenomegaly was associated with MEFV gene mutation, more often with homozygotes for *M694V*, as well as with FMF severity.

No studies reported an association between FMF and *nonamyloid liver* disease. However, the recurrent transient mild hyperbilirubinemia (mainly indirect) (0.2%) or mild elevation of transaminases in the course of FMF have been described. These changes occurred only during the peritoneal attacks and lasted for 1-2 days [*Majeed H. et al., 1999*]. In attacks mild to moderate hepatomegaly (up to 3-4 *cm*), as well as transient jaundice were reported due to biliary dyskinesia [*Ayvazyan A., 1982; Astvatsatryan V., Torosyan Y., 1989; Friedman S., Janovich H., 1998; Majeed H. et al., 1999; Tweezer-Zaks N. et al., 2007*]. Morphologically sinusoids dilatation and hyperemia without inflammatory cells and fibrosis were observed [*Ter-Kasparova M., 2002*].

The possible relationship between *cryptogenic cirrhosis* (CC) and FMF was studied [*Tweezer-Zaks N. et al., 2007*]. Significantly high frequency of CC in Jewish FMF patients from Israel (mainly in homozygotes for *M694V)* compared to cirrhosis of all types expected in the total population of Israel (0.15% *vs* 0.015%) was revealed. *MEFV* might serve as a modifier gene in CC and the genetic analysis in patients with CC unrelated to FMF, particularly patients of Mediterranean origin, may be warranted [*Tweezer-Zaks N. et al., 2007*].

In FMF attacks mild liver enlargement (2 *cm* below the right costal margin) was revealed in 126 (17.7%) of observed patients. In 5 (0.7%) patients mild hyperbilirubinemia and in 4 patients (0.6%) mild isolated hypertransaminasemia occurred during attacks and rapidly disappeared upon colchicine therapy. The frequency of hepatomegaly was not associated with the genotype (c^2=1.83; p>0.05) (Figure 1). However, liver enlargement was more often in homozygotes for M694V/M694V genotype (21.8%; in 46 out of 47 homozygotes) compared to compound-heterozygotes for M694V/M680I (18.2%) and M694V/V726A (15.6%). The frequency of hepatomegaly correlated with the severity of FMF (c^2=14.72; p<0.0001). It significantly increased (2.55 times) in a severe course compared to mild activity of the disease (OR: 2.55; 1.03÷6.40; p<0.05).

Thus, the risk of hepatomegaly and its degree were associated with the severity of FMF course and did not depend on the MEFV gene mutations. More often it was noticed in homozygotes for M694V (694V/M694V) and compound-heterozygotes for M694V/M680I and M694V/726A genotypes.

3. FMF associated or coexisting diseases affecting the alimentary tract

It is well-known that four types of vasculitides are associated with FMF, although FMF is not an autoimmune disease [*Ozdogan H. et al., 1997*]. Henoch-Shonlein purpura (HSP) has been reported in 3-5% of children with FMF, Behcet disease (BD) in 4%, *Polyarteritis nodosa* (PAN) in 1%, Protracted febrile myalgia (PFM) in 0.5% of FMF patients. Though a small group of vasculitides in FMF (~ 3%), these diseases are characterized by a high frequency compared to the frequency of vasculitis in the general population [*Mor A. et al., 2003*]. MEFV gene mutations considered as a genetic factor involved in pathogenesis of these vasculitides, based on impaired immune response in healthy carriers of MEFV gene mutations [*Balbir-Gurman A. et al., 2007*]. Main GI features of vasculitis are severe abdominal pains, bloody diarrhea, GI-bleeding, rarely – the ileoileal intussusception [*Ozdogan H. et al., 1997; Mor A. et al., 2003*]. High prevalence of the GI tract vasculitis among FMF patients is supposed because of high frequency of occult blood in the stool specimens after attacks [*Ozdogan H. et al., 1997*]. Despite the typical manifestations of the disease, FMF-associated vasculitides have more severe course, which complicates differential diagnosis; mostly these cases are treated with steroids.

We observed 31 (4.3%) patient with *FMF-associated vasculitis*. In 11 (1.5%) patients FMF was associated with HSP, in 19 (2.7%) children - with PFM, occasionally, in 1 (0.1%) - with BD. All these patients had early manifestation (before 2.6-3 years) and severe course of typical FMF ($F = 0.015$) (RR: 3.90; CI: 1.32÷11.35; c^2=5.94; p=0.015). The genetic analysis more often revealed a severe *M694V* mutation, mainly in homozygous genotype. FMF association with HSP and PFM have been observed, correspondingly, in 2.9% patients and in 4.6% of homozygotes for M694V mutation (c^2=8.27; p<0.02), which indicate the influence of M694V/M694V genotype in the development of these vasculitides (Figure 2).

Thus, the frequency of FMF-associated vasculitides was associated with homozygous for *M694V* genotype (M694V/M694V), as well as with the high disease severity. HSP and PFM might be considered possible markers of severe course of FMF. These results confirmed the predisposition of FMF patients to vasculitides in a population with high prevalence of FMF [*Lange-Sperandio B. et al., 2004*]. We consider that Armenian children with HSV, PFM or other vasculitides should be tested for MEFV gene mutations even in the absence of typical FMF symptoms.

FMF and *Inflammatory Bowel Disease (IBD): Crohn's disease (CD) and Ulcerative Colitis (UC),* are inflammatory disorders sharing some commom clinical features: periodicity and relapse of main clinical symptoms (abdominal pain attacks, arthritis), abdominal inflammation with infiltration by neutrophils at the site of injury, disregulation of apoptosis [*Dervichian M. et al., 2003; Giaglis S. et al., 2006*]. IBD appears to be more prevalent in FMF matched ethnic populations (0.5% *vs* <0.1% in non-Ashkenazi Jewish) and presents later than in patients without FMF [*Cattan D. et al., 2000; Fidder H. et al., 2002*]. FMF in this group of patients shows a higher attack frequency and is more often complicated by amyloidosis [*Fidder H. et al., 2002*]. The increased frequency of MEFV gene mutations with the prevalence of *M694V* in UC patients, especially in those with episodic arthritis, as well as the E148Q mutation in CD patients with perianal lesions was reported in some studies [*Karban A. et al., 2005; Giaglis S. et al., 2006*]. Despite the increasing number of reports on possible associations between IBD and FMF (commom clinical symptoms, high frequency of CD in FMF patients, etc.), some controversy exists: whether there is any associ-

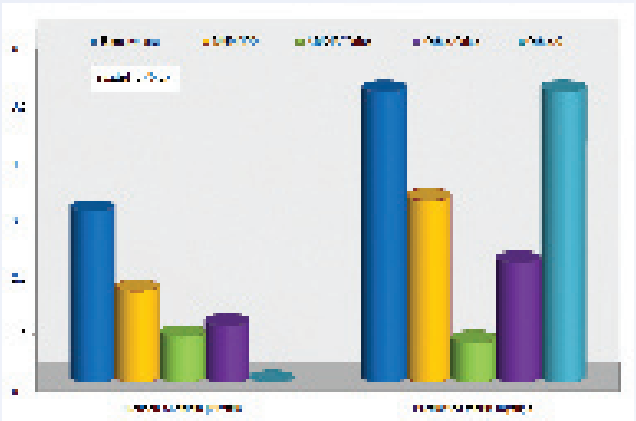

Figure 2. *The risk of vasculitis and genotypes in children with FMF (shaded p <0.05).*

ation between these conditions, or it is just a co-existence with FMF. The role of genetic factors associated with inflammatory diseases is not finally clarified as well. Based on the recent investigations, it has been supposed that genes associated with inflammatory disorders might have a modifying effect to each other. Namely, NOD2/CARD15 gene associated with CD was found to be proximity to MEFV gene in the short arm of chromosome *16m*. Moreover, the two genes are thought to have a role in the regulation of apoptosis, cytokine processing and inflammation. MEFV gene as a modifier may affect the expression of CD/IBD (or other inflammatory disorders), and, alternatively, CD-associated NOD2/CARD15 gene may trigger FMF [*Gumucio D. et al., 2002; Fidder H. et al., 2005; Sinan S. et al., 2007*].

Amongst 715 FMF patients, 3 children (0.5%) were found with concominant *ulcerative colitis* (*UC*)**.** These patients had early and atypical onset of disease during the first year of life: the recurrent febrile abdominal colics and/or episodes of diarrhea and/or abacterial haemocolitis, and later on – myalgia, arthritis, and polyserosites. The patients had severe course of both diseases, FMF and UC, they were homozygous for M694V mutation and resistant to treatment of UC. After initiation of high-dosage colchicine therapy (0.06-0.07 *mg/kg/day*), the long-lasting remission of both diseases has been achieved and the steroid/immunosuppressive therapy was stopped.

Our results confirmed the suggestion that the early onset of UC (especially during the 1st year of life) in ethnically matched populations should be indicative for *MEFV* mutations analysis [*Sari S. et al., 2007*]. Further studies are needed to determine the frequency of UC and CD in Armenian children with FMF, the influence of different MEFV gene mutations on IBD course, as well as the role of colchicine in treatment of these diseases.

4. FMF abdominal and digestive system manifestations related to the amyloidosis

FMF amyloidosis (phenotype 1) is a severe complication of FMF, mainly presented as the most clinically significant amyloid nephropathy and renal failure, usually in untreated patients. In systemic amyloidosis GI tract is one of the main sites of amyloid depositions (type AA) early in the course of FMF. But clinical symptoms of amyloidosis occur in some patients after many years of asymptomatic amyloid deposition [*Livneh A. et al., 1999; Mor A. et al., 2003*]. The manifestations of GI tract amyloidosis are untreatable diarrhea, steatorhhea, severe malabsoption, the main mechanism of which are disturbances of bile acid deconjugation due to decreased intestinal motility and bacterial overgrowth [*Friedman S., Janovich H., 1998*]. Rare complications are chronic ischemic colitis and chronic obstruction or perforation of the large intestine, secondary to amyloid deposition and formation of fibrotic mass in the colon. In late stages of the systemic amyloidosis the amyloid deposits are limited to the portal vascular structures; parenchyma of the liver usually is not involved; clinical and laboratory peculiarities are mild hepatomegaly, well-preserved hepatocellular function [*Friedman S., Janovich H., 1998*]. Among 34 patients with FMF kidney amyloidosis in the Department of Nephrology, Dialysis, and Kidney Transplantation of "Arabkir" Medical Center diarrhea was observed mainly in patients at the end-stage of kidney disease: on dialysis and after transplantation.

5. Digestive system manifestations as adverse effects of colchicine treatment

Long-term daily oral colchicine therapy is the only and relatively safe treatment of FMF, which prevents systemic as well as renal amyloidosis and improves the quality of life in patients [*Livneh A., Langevitz P., 2000*]. Because of the low therapeutic index, colchicine is also considered as a potentially toxic drug and requires constant control and dose correction [*Jayaprakash V. et al., 2007*]. The adverse effects of colchicine treatment are mainly of GI origin and reversible, dose dependent, rare and may disappear after decreasing the dosage of colchicines. The most frequent side effect is diarrhea, less often – nausea, hyperperistalsis, vomiting [*Mor A. et al., 2003; Rigante D. et al., 2006*]. Diarrhea as a side effect of colchicine therapy results from diminished activity of intestinal enzymes (lactase, maltase, sucrose), decreased absoption of D-xylose and vitamin B_{12}, increased fecal excretion of starch,

fat and bile soluble vitamins. Partially it might be presented by steatorrhea and lactose deficiency. The main practical issue is to differentiate amyloid-induced diarrhea from colchicine-induced one [*Ehrenfeld M. et al., 1982; Mor A. et al., 2003*].

In 7 (1%) children with FMF we observed side effects of colchicine that were presented mainly as diarrhea (6) and erythematous rush (1). Diarrhea was dosage-dependent and disappeared after decreasing colchicine dosage; most patients were M694V mutation carriers.

CONCLUSIONS

The risk for development of the FMF *abdominal febrile attacks* was associated with homozygotes for *M694V* mutation, as well as compound-heterozygotes for three main mutations: M694V, M680I, V726A.

Besides the typical peritoneal crises, a number of other abdominal and digestive system manifestations of FMF have been observed: adhesive intestinal obstruction (AIO) (3.2%), hepatomegaly (17.7%), splenomegaly (9.9%), concominant ulcerative colitis (UC) (0.4%), as well as FMF-associated vasculitis: protracted febrile myalgia (PFM) (2.7%), Henoch-Shonlein purpura (HSP) (1.5%), Behcet disease (BD) (0.1%). Some of them were more frequent than expected. The frequency of AIO, vasculitides was associated with M694V homozygous genotype, high disease severity, early disease onset and delayed diagnosis. Patients with UC also were M694V homozygotes; they had atypical onset of disease during the first year of life: recurrent febrile colics, diarrhea and/or abacterial haemocolitis, later accompanied with myalgia, arthritis, polyserosites, and were resistant to treatment of UC. FMF patients with the severe course of disease and M694V mutation carriers, especially those with homozygous genotype, are at a high risk for abdominal and digestive system manifestations. Some of them (AIO, UC, splenomegaly) might be considered as possible markers of severe course, even in the absence of typical FMF symptoms. They might be the early, first and only manifestations of FMF.

Considering the high prevalence of FMF in Armenia, we believe that the genetic screening for FMF should be indicated for children with some gastrointestinal manifestations: adhesive (mechanical) intestinal obstruction, FMF associated vasculitides (HSP, PFM, BD); inflammatory bowel disease (UC, CD), splenomegaly of an unknown origin, recurrent abdominal pains, especially in case of early disease onset, atypical presentations and resistance to treatment.

Awareness on digestive system associations of FMF might improve earlier diagnosis, treatment of disease and prevention of amyloidosis.

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