Familial Mediterranean Fever in a Sample of Iraqi Patients

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ABSTRACT:

BACKGROUND:

Up to the best of my knowledge, despite the fact that Arabs have a high prevalence of Familial Mediterranean fever (FMF) and its gene, little information is available about the natural history of this disease in Iraqi population.

OBJECTIVE:

This study had been designed to clarify the natural of FMF among Iraqi people.

METHODS:

This study is a Follow up (cohort) study that enrolled 23 patients with FMF, 17 of them were male. The sample had been randomly selected from those had attended Al – Shaheed Al – Sadr Hospital (Baghdad / Iraq) during the period from the first of April, 2003 to the 31st of March 2005. All of the patients had been subjected to thorough physical examination and all of the required investigation had been done.

RESULTS:

Age of the patients who had been included in this study ranged between (14 – 59) year old (21.57 + 18.7 year old). All of them were Arab Muslims. Fever and abdominal pain had been observed in all of the patients included in this study at variable time during the disease course. All of the patients included in this (23 patients) had responded well to colchicines treatment (dose of 2 mg/ day). Statistical analysis revealed a significant reduction in the number of attacks per year with the use of prophylactic colchicines (calculated $t = 3.94$, p value < 0.005).

CONCLUSION:

This study had shown that Iraqi Arabic population might have a batter survival and less risk, if present, of developing amyloiedosis and all of its sequelae. This point needs to be clarified more by doing much larger studies that enroll larger number of Arabs population and for longer period .furthermore, this study had indicated that colchicines is effective in reducing the number of attacks of familial Mediterranean fever per year of follow-up in addition to its efficacy in relieving the acute attack.

KEYWORDS: Familial, Mediterranean, Arab, Colchicines

INTRODUCTION:

In 1908, Janeway and Mosenthal described a Jewish girl who had episodic abdominal pain and fever. Although additional cases were described subsequently, it took nearly half a century to establish this disorder as familial Mediterranean fever [1-4]. The condition is characterized by short attacks of serositis (peritonitis, pleuritis, or arthritis) and fever[5]. Familial Mediterranean fever is an autosomal recessive disease, affecting more than 10,000 patients worldwide. It predominantly affects people from the Mediterranean basin, including Sephardic Jewish, Arabs, Turks, and Armenian[1]. However, frequency in any location is a function of the ethnic background of the patient[6]. This phenomenon is evident in that the familial Mediterranean fever have a prevalence of 1 case per 73,000 population among Ashkenazi Jewish people (descended from Eastern European Jewish people) with a gene frequency of 1: 135, while among Sephardic Jewish people (most of them had descended from Middle East), the Prevalence is 1 case per 250-1000 population, with a gene frequency of 1:8-16. Furthermore, Arabic people may have a prevalence of 1 case per 2600 population in children and a gene frequency of 1:50[6-10]. Familial Mediterranean fever is a clinical diagnosis. If the patient has a characteristic medical history and belongs to an ethnic group with a high prevalence of the disorder, the diagnosis is not difficult to make [11]. Since 1972, colchicine has been the first-line treatment for patients with familial Mediterranean fever and its efficacy has been established by two controlled clinical trials [12-13]. The prognosis of patients with familial Mediterranean fever is determined mainly by the presence or absence of AA amyloidosis, in its absence, life expectancy is normal. Treatment with colchicine greatly altered the prognosis by arresting amyloidosis and reversing proteinuria [1].

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Up to the my best knowledge, despite the fact that Arabs have a high prevalence of the familial Mediterranean fever and its gene, little information is available about the natural history of this disease in Iraqi population. This study had been designed to clarify the natural history of familial Mediterranean fever among Iraqi people, to detect the frequency of different clinical manifestations, to find the frequency of amyloidosis or proteinuria, to assess the disease activity in term of its effect on the acute phase reactant (erythrocyte sedimentation rate, white blood cell count and C-reactive protein), and to assess the effect of colchicine therapy in relieving the acute attack and in preventing these attacks if it was used in its prophylactic dose.

PATIENTS AND METHODS:

This study is a follow up (cohort) study that enrolled 23 patients with FMF, 17 of them were male. The sample had been randomly selected from those had attended Al-Shaheed Al-Sader hospital (Baghdad / Iraq) during the period from the first of April, 2003 to the 31st of March 2005 . All of the patients had been subjected to thorough physical examination and all of the required investigations had been done. All the data collected processed and formulated in frequency distribution tables. Statistical analysis had been performed when required using student's t-test with a p value of 0.05 as a level of statistical significance.

RESULTS:

This study had enrolled 23 patients with familial Mediterranean fever, including 17 male patients (73.9% of the sample) and 6 female patients (26.1% of the sample). Age of the patients who had been included in this study ranged between 14-59 year old (21.57 ± 18.7 year old). Twenty one out of the 23 patients included in this study (91.3 % of the sample) were younger than 30 year-old. Table-1 shows patients distribution according to their age.

Regarding the ethnic origin of the patients who composed the sample of this study, all of them were Arab Muslims. Family history of Mediterranean fever had been detected in 9 patients (39.1% of the sample).

On reviewing the clinical features that had been observed in the sample of this study, fever and abdominal pain had been observed in all of the patients included in this study at variable time during the disease course. In contrast, no one of them had features suggestive of skin lesions related to familial Mediterranean fever. Figure-1 shows patients distribution according to the observed clinical features of familial Mediterranean fever.

In addition, proteinuria had not been detected in any of the patients included in this study. Erythrocyte Sedimentation Rate (ESR) was more than 20 mm/hr in 20 out of the 23 patients enrolled in this study (86.9% of the sample), with a range of 27-84 mm/hr. Similarly, White blood cell count was greater than 12 X 10^3/mm^3 in the same percentage of patients (20 patients, 86.9% of the sample) and had a range of 12.2-16 X 10^3/mm^3. Furthermore, C-reactive protein had been positive in all of the patients (100% of the sample).

In regard to the effect of colchicine therapy in the acute attack, all of the patients included in this study (23 patients) had responded well to colchicine treatment (dose of 2 mg/day) in term of relieving of febrile attacks and improvement in the values of ESR, WBC count and C-reactive protein. By using colchicine as prophylactic therapy in a dose of 0.6 mg/day, the mean number of attacks during the first year of prophylactic therapy with colchicine was 0.39 attack/year, with a range of 0-2 attack/year. In the other hand, the number of attack per year prior to the use of prophylactic colchicine had ranged between 2-5 attack/year, with a mean of 2.6 attack/year. Twenty out of the 23 patients used the prophylactic dose had good response to this prophylaxis (86.9% of the sample). This good response to prophylactic therapy was in term of significant reduction in the number of acute attacks in its different form per year of follow-up. Figure-2 shows patients distribution according to their response to colchicine prophylactic therapy in a dose of 0.6 mg/day. Statistical analysis revealed a significant reduction in the number of attacks per year with the use of prophylactic colchicine (calculated t = 3.94, p value < 0.005).

Table1: Patients distribution according to their age

Age(year-old)	No.	%
< 20 year old	13	56.5%
20-29	8	34.8%
30-39	1	4.35%
40-49	0	0%
50-59	1	4.35%
Total	23	100%
Range	41-59 year-old	
Mean ± SD	21.57 ± 18.7 year old	

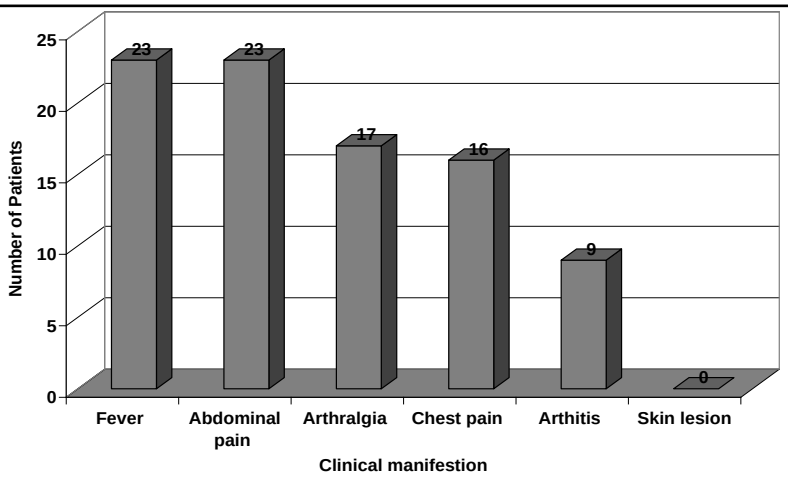

Figure-1: Patients distribution according to their clinical manifestation of FMF

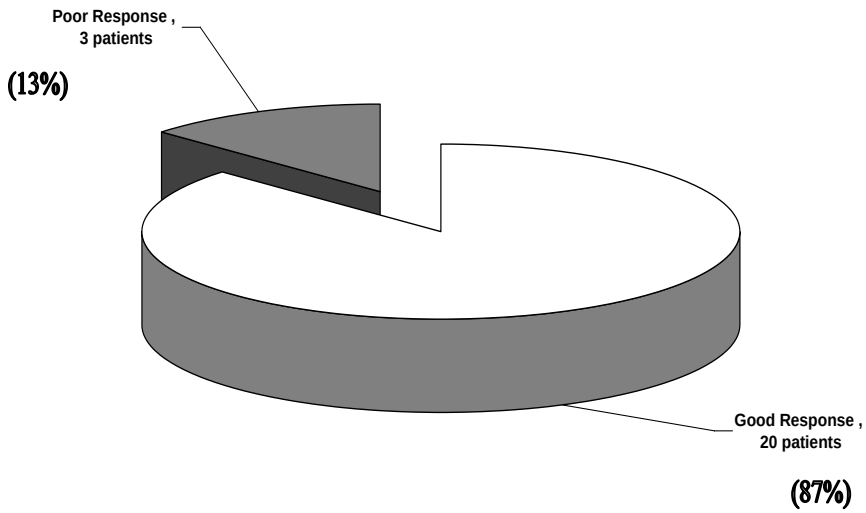

Figure-2: Patients distribution according to their response to colchicine prophylaxis

DISCUSSION:

Amyloidosis can be considered as one of the main factors that determine the prognosis of patients with familial Mediterranean fever. Amyloidosis manifests itself by proteinuria or overt nephrotic syndrome[1]. This study revealed that no one of the patients who had been included in it had neither proteinuria nor nephrotic syndrome. This finding can be explained by two ways. The first is related to the effect of use of colchicine as treatment for the acute attack or as prophylaxis. The second explanation is that it can be related to that all of the patients included in this study were Arabs and Muslims. It is well documented that before the institution of colchicine therapy, mortality from amyloidosis and nephritic syndrome was almost universal by age 50 years in North African Sephardic Jewish patients[6]. Colchicine therapy had been established to be able to prevent the development of amyloidosis[14-17]. The role of colchicine in treating patients with familial Mediterranean fever is far beyond the relieve of the acute attack only, it extends to improve the life expectancy of patients with this disease and improves their quality of life. Before the introduction of colchicine, amyloidosis occurred in 60% of affected patients who were over 40 year of age, and it was the main cause of death in such patients [19]. Treatment with colchicine greatly altered the prognosis by arresting amyloidosis and, in addition, reversing proteinuria [1].

However, there is still some sort of controversy about the role of colchicine treatment in the prevention of febrile attack. Three double blind clinical trials performed in the early 1970s showed that daily administration of 1-2 mg colchicine prevents febrile attacks in familial Mediterranean fever[15-17]. This study revealed that 20 out of the 23 patients used the prophylactic dose had good response to this prophylaxis (86.9% of the sample), this response was in term of absence of febrile attacks. Statistical analysis revealed a significant reduction in the number of attacks per year with the use of prophylactic colchicine (calculated $t = 3.94$, p value < 0.005). These percentages of complete and partial remission (response) is much better than the results of other series of 350 children, in which colchicine induced complete remission of the attacks in 64% of the patients and partial remission in 31% of the patients[20]. Moreover, colchicine can consistently abort attacks of familial Mediterranean fever if taken at the onset of symptoms [21].

An ability that can support the result of this study which showed than all of the patients who had used colchicine at the onset of the attacks, had complete remission from attacks of familial Mediterranean fever. In the other hand, some authors like AR Allen and colleagues stated that while colchicine prevents the development of renal amyloidosis in familial Mediterranean fever, it does not abolish febrile attacks[15]. Even this argument can not affect the satisfying effect of colchicine therapy on the short and long term life expectancy and quality in patients with familial Mediterranean fever depending on the well established fact that even if colchicine therapy does not prevent febrile attacks, it will at least prevent amyloidosis which can be considered as the main killer of patients with familial Mediterranean fever and the main factor that affect the morbidity of them [22].

In addition to the effect of colchicine therapy on the risk of having amyloidosis in patients with familial Mediterranean fever, this risk had been shown to be variable according to the ethnic origin of the studied population. In pre-colchicine era, several studies and authors showed that the risk of amyloidosis is much higher among North African Sephardic Jewish and being extremely rare among other Sephardic Jewish, Ashkenazi Jewish, and Armenian patients. Unfortunately no pre-colchicine-therapy data are available from Arabic patients [1,6-7]. This study shown that C-reactive protein was the most frequently elevated acute phase reactant (it was positive in all of the patients included in this study). C-reactive protein had been followed by the ESR and WBC count in term of frequency of elevation (20 out of 23 patients, 86.9% of the sample for each respectively).

This finding is similar to what had been shown by Korkmaz C and his colleagues in their study which revealed that C-reactive protein was the only acute phase protein that was increased in all attacks, and it was followed in frequency by ESR (88%), fibrinogen (63%) and WBC (50%)[23].

This study showed that only 56.5% of the patients included in this study was in their 2nd decade of life. This number is quite less than what shown by other studies which revealed that abut 90% of patients have their first attack before the age of 20 years [1,24]. This higher percentage of older patients in this sample might be related to that familial Mediterranean fever might be less severe among Arabic population, as this proposal can be suggested by the absence of amyloidosis, which is the main bad prognostic factor, observed in this study. Furthermore, attacks of familial Mediterranean fever usually unfold suddenly, and the symptoms persist for only a short time (6-96 hours)[1]. Therefore, taking into consideration the nature of health education in Iraqi population, the symptoms might resolve before making the patient seeks medical help.

In addition, familial Mediterranean fever might present to the medical system and it might be misdiagnosed, as it can present as acute abdomen for example. Abdominal pain of one or two days' duration occurs in 95% of patients, and can present as acute abdomen, although some patients have only mild abdominal pain without overt peritonitis[25]. In addition, the clinical manifestation of familial Mediterranean fever, characteristically, are accompanied by fever, but patients may present with fever alone [1]. Table-2 shows comparison between the frequencies of the clinical manifestation noticed in the sample of this study with that observed in other similar studies.

CONCLUSION:

This study had shown that Iraqi Arabic population might have a better survival and less risk, if present, of developing amyloidosis and all of its sequelae. This point needs to be clarified more by doing much larger studies that enroll larger number of Arabs population and for longer period. Furthermore, this study had indicated that colchicine is effective in reducing the number of attacks of familial Mediterranean fever per year of follow-up in addition to its efficacy in relieving the acute attack.

Table 2: Comparison between the frequencies of different clinical manifestation noticed in this study with that observed from other similar studies.

Clinical manifestation	This study	Other studies
Fever	100%	100% [5, 25-26]
Abdominal pain	100%	95%[25]
Arthritis	39.1%	75%[25]
Chest pain	69.5%	30%[5]
Skin lesions (erysipelas-like skin lesions on the shin or feet)	0%	7-40% [26]

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