The emerging issue of cardiovascular involvement in familial Mediterranean fever

Commentary on

Vasculitis, left bundle branch block, and Raynaud's phenomenon as a manifestation of familial Mediterranean fever

Giuseppe Cocco

Arch Med Sci 2008; 4, 4: 460–464

Armen Yuri Gasparyan[1], Murat Ugurlucan[2]

[1]Dudley Group of Hospitals, NHS, Dudley, West Midlands, United Kingdom
[2]Department of Cardiac Surgery, University of Rostock, Rostock, Germany

Submitted: 27 November 2008
Accepted: 30 November 2008

Arch Med Sci 2008; 4, 4: 465–467

Corresponding author:
Murat Ugurlucan, MD, FASA
Department of Cardiac Surgery
University of Rostock
Bergstrasse 7a, No: 105
18057 Rostock, Germany
Phone: + 90 535 431 67 86
Fax: + 90 212 235 25 68
E-mail:
muratugurlucan@yahoo.com

Familial Mediterranean fever (FMF) has long been viewed as a disease with mild, functional cardiovascular involvement which has no impact on outcomes of the disease [1, 2]. Kidney involvement over the course of chronic uncontrolled inflammation leading to systemic amyloidosis A has been estimated as a major threat for patients [3]. Amyloidosis associated with FMF had a dramatic effect on kidney function in the pre-colchicine era and the majority of patients with FMF died of end-stage renal failure. Clinical and pathomorphological investigations at different stages of systemic amyloidosis in this disease suggested that affection of the heart was associated with kidney function impairment and progressive course of amyloidosis.

As one of the striking features of cardiovascular morbidity in FMF, cardiac amyloidosis, either isolated, which is quite rare, or in combination with involvement of other organs and systems, can exist in any FMF patient, particularly in the case of prolonged course of the disease and neglect of appropriate suppression of amyloidogenesis by colchicine therapy [4]. Prognostic significance of cardiac involvement in systemic amyloidosis due to FMF is still not clarified, though it is plausible that accumulation of amyloid fibrils in the conductive system, the myocardium, valves and microvascular beds may substantially worsen systemic blood circulation due to restrictive cardiomyopathy, and a wide range of life-threatening arrhythmias, each bearing substantial negative prognostic value.

In a series of recent observational studies attempts were made to explore associations between production of numerous inflammatory and immune biomarkers and risk of accelerated course of atherosclerotic vascular disease in FMF [5]. With certain success it was shown that over-production of these biomarkers during inflammatory attacks of the disease and, more importantly, continuous inflammatory response in between attacks, may put patients at risk of accelerated atherosclerosis with premature manifestation of ischaemic heart disease and myocardial infarction, in particular. Importantly, based on previous numerous small observational studies and published clinical cases of premature manifestation of cardiovascular disease in FMF, it is hypothesized that

FMF with its low-grade inflammation in between attacks is an ideal clinical model for investigation of pathophysiological links between inflammatory markers and atherosclerotic disease in the general population. In this regard, it seems especially important to investigate the association between C-reactive protein, which is constantly raised in about two-thirds of patients with FMF, and atherosclerotic disease [6].

Inflammation and disturbances in the immune response characteristic for FMF can predispose not only to amyloidosis and atherosclerosis, but also to a number of other inflammatory and autoimmune disorders with cardiovascular involvement. Clinical observations are suggestive of highly probable transformation of FMF into other rheumatic diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, seronegative spondyloarthritis) or concurrent course of FMF with inflammatory bowel disease, Behçet's disease, *Schönlein-Henoch purpura*, *polyarteritis nodosa* or other vasculitides [7, 8]. Obviously, the risk of life-threatening cardiovascular disease in FMF can multiply once the patient develops vasculitis. Actually, in the case of vasculitic co-morbidities the risk of coronaritis, coronary aneurysms with manifestation as myocardial infarction, is clinically relevant and should prompt the clinician to aggressively suppress inflammation with colchicine and, perhaps, other immune regulatory drugs alongside the therapy used for acute coronary syndromes.

As far as coronary pathology in FMF is concerned, one should carefully consider atherosclerotic vascular disease, which has a subclinical course in most patients with FMF and becomes more overt with age. It is noteworthy that coronary aneurysms, coronaritis and coronary thromboembolism should be suspected in patients with vasculitic co-morbidities and proper investigation should be performed.

Another big issue related to cardiovascular disease in FMF, but still not largely investigated, is how colchicine, a currently available, relatively effective and safe means for persistent suppression of inflammation, preventing attacks and amyloidosis in FMF, influences myocardial and coronary structural and functional characteristics. In a retrospective study of prevalence of ischaemic heart disease and cardiovascular risk factors in FMF it was shown that continuous colchicine therapy improves cardiovascular risk profile of patients and makes them comparable to healthy subjects [9]. Additionally, in some case-control studies with FMF patients taking colchicine there were no significant differences in the magnitude of subclinical atherosclerosis between patients and healthy subjects [10]. This, to some extent, suggests a beneficial effect of colchicine on the course of atherosclerosis and cardiovascular disease in FMF. Moreover, one would expect significantly decreased prevalence of inflammatory and autoimmune co-morbidities, including vasculitides, in FMF patients maintained on regular colchicine therapy since the onset of the disease. Although there has not been any prospective cohort study to prove or exclude that, promising results of clinical use of colchicine worldwide since the first report published in 1972 [11] and understanding of common pathophysiological features shared by polyserositis and other so-called pleiotropic manifestations of FMF make it, at least for the time being, justified to recommend regular life-long colchicine therapy to avoid not only serositic attacks and amyloidosis, but cardiovascular manifestations as well.

In the review and presentation of a rare case of cardiovascular involvement in FMF by Cocco [12] the author described transient left bundle branch block (LBBB) which disappeared after three months of successful treatment with colchicine. This, to some extent, indicates an association of coronary vascular pathology with inflammation linked to FMF. However, manifestation and combination of several symptoms of rheumatic disease in the presented patient, i.e. intensive and lasting myalgia, arthralgia, migrating pain and joint stiffness, rash on the abdomen and the back, petechial spots and purpura on both calves, Raynaud's syndrome, high level of anti-neutrophil antibodies with perinuclear staining pattern and specificity for myeloperoxidase, indicate complexity of associations between FMF and LBBB. After all, it is unclear whether LBBB was solely related to FMF or systemic vasculitis also played a pathogenic role. Moreover, atherosclerosis and amyloidosis could also play some role in coronary vasculopathy. Relevant cardiovascular investigations and rectal biopsy for amyloidosis could provide more information in this respect. Hepatosplenomegaly was noticed on physical examination, which could be due to either flair of FMF or systemic amyloidosis. In the latter case this sign would be more persistent and could be part of the severe course of FMF as described by the author.

The last, but not least important issue is appropriateness of the treatment chosen in this particular case. It is well known that colchicine can be effective in FMF at doses not less than 1-2 mg/day and the sooner it is administered, the less probable will be amyloidosis, and the better will be clinical course of FMF. Although steroid therapy is not widely recommended in FMF, in the presented case it could improve some of the symptoms, and in particular could have a beneficial effect on the course of myalgia.

In conclusion, the presented case once again underlines the importance of careful monitoring of heart functions in FMF, which can develop a wide range of cardiovascular disorders.

References

1. Gasparyan AY, Petrosyan AH. Cardiovascular involvement in familial Mediterranean fever. Cardiovasc Ther Prev 2007; 6: 117-24.
2. Nazaretyan EY, Gasparyan AY. Contemporary issues of periodic disease. Med Sci Arm 2000; 40: 35-41.
3. Ben-Chetrit E, Levy M. Familial Mediterranean Fever. Lancet 1998; 351: 659-64.
4. Gasparyan AY, Nazaretyan EY, Narimanyan MZ. Predominant cardiac lesion in periodic disease (familial Mediterranean fever). Russ Fam Phys 2001; 5: 50-3.
5. Akdogan A, Calguneri M, Yavuz B, et al. Are familial Mediterranean fever (FMF) patients at increased risk for atherosclerosis? Impaired endothelial function and increased intima media thickness are found in FMF. J Am Coll Cardiol 2006; 48: 2351-3.
6. Korkmaz C, Ozdogan H, Kasapçopur O, Yazici H. Acute phase response in familial Mediterranean fever. Ann Rheum Dis 2002; 61: 79-81.
7. Korkmaz C, Zubaroglu I, Kaya T, Akçar N, Gürbüz E, Ozen S. A case of familial Mediterranean fever, Behçet's disease and polyarteritis nodosa complicated by perirenal haematoma. Clin Exp Rheumatol 2001; 19 (5 Suppl 24): S78-9.
8. Hatemi G, Masatlioglu S, Gogus F, Ozdogan H. Necrotizing vasculitis associated with familial Mediterranean fever. Am J Med 2004; 117: 516-9.
9. Langevitz P, Livneh A, Neumann L, et al. Prevalence of ischemic heart disease in patients with familial Mediterranean fever. Isr Med Assoc J 2001; 3: 9-12.
10. Sari I, Karaoglu O, Can G, et al. Early ultrasonographic markers of atherosclerosis in patients with familial Mediterranean fever. Clin Rheumatol 2007; 26: 1467-73.
11. Goldfinger SE. Colchicine for familial Mediterranean fever. N Engl J Med 1972; 287: 1302.
12. Cocco G. Vasculitis, left bundle branch block and Raynaud's phenomenon as a manifestation of familial Mediterranean fever. Arch Med Sci 2008; 4: 460-4.