WHAT ADVANTAGE DID THE HETEROZYGOTES FOR MEFV MUTATIONS HAVE – IF ANY?

Seza Ozen

Familial Mediterranean fever (FMF) is auto-inflammatory diseases characterized by recurrent attacks of fever and serositis accompanied with an augmented acute phase response (1-5). The mutated protein in this genetic disease is expressed mainly in the neutrophils and monocytes (6). FMF is known to be very common among Arabs, Armenians, Jews and Turks. The historic trace-back of the shared haplotype and common mutations suggests a common ancestor at least 2000 years ago, when most of these populations were living together in the eastern Mediterranean basin, around Mesopotamia (1,4).

The presence of multiple founder mutations with high prevalence in certain ethnic populations of today, raises the possibility of a selective advantage for carriers of these mutations, similar to the heterozygote advantage of sickle cell trait against malaria (1,5). Indeed, the carrier frequency for the mutations in MEFV is as high as 1/3, 1/5 and 1/5 among Armenians, Jews and Turks, respectively (5, 7-9). The exceptionally high gene frequencies for FMF in more than one population could be explained by increased resistance to a specific organism(s) that may have been endemic in the area then (1); it has been suggested that the role of pyrin in the control of inflammation maybe consistent with heterozygotes exhibiting heightened response to certain organism(s).

Mansfield et al (10) have shown that pyrin is expressed in microtubuli, that would selectively have an effect on intracellular killing. The first farmers of mankind are known to have settled some 8000 years ago in the ‘Fertile crescent’, extending from Mesopotamia to Anatolia. On the other hand, tuberculosis is an ancient disease caused by tubercle bacillus, which is an intracellular pathogen. Mycobacterium would have been a new disease for the first farmers. We hypothesized that an increased resistance to mycobacteria could be the advantage of the carriers for MEFV mutations (11). However, our study has shown that the frequency of heterozygotes was not different among the Tuberculosis patients as compared to healthy Turkish controls (11).

It has been shown and observed by many of us that individuals with one mutation have elevated C-reactive protein (CRP) levels suggesting an increased acute phase inflammatory response that might have conferred a certain advantage in these people (12).

It has also been suggested that the heterozygotes had a possible protection against asthma (13). Indeed, when we questioned parents of our patients with definite FMF, we found that only 3 out of the 100 parents described a history of probable asthma (which was significantly less than the frequency in the Turkish population), only one described allergic rhinitis and there was no allergic eczema in this cohort.

However, our recent studies suggest that the decreased allergic responses in FMF patients and carriers maybe a result and not the cause of the underlying pathophysiology. We have studied the T helper-1 (Th1) /T helper-2 (Th2) cytokine profile in FMF patients and in carriers of MEFV mutations: the intracellular staining for interferon-gamma (IFN) and interleukin-4 were analyzed for Th1 and Th2 responses, respectively (14). We have found that there was a predominant and marked Th1 response in these heterozygotes when compared to age-matched controls (14). Thus it may be speculated that heterozygotes were selected because they were protected against allergies introduced with the settled lifestyle. However, allergy is not a fatal disease and one wonders whether this was just a bystander effect rather than the cause of the selection.
Thus the advantage of the carriers to be selected in biblical times may be simply that these patients were able to mount a better, IFNγ dependent, Th1 inflammatory response that might have helped them better react with certain pathogen(s) they encountered (14).

On the other hand Kogan et al (15) claimed an absence of a perceptible biological advantage for the carrier state showing that the carriers of the MEFV mutations had an excess of febrile episodes. Furthermore Booth et al (16) and subsequently we (unpublished data) have shown that the MEFV mutations were increased among severe inflammatory arthritis patients.

These and other relevant data suggest the pay off for the advantage –if any?- offered with a MEFV mutation, may have been an increased susceptibility to inflammation. Understanding the exact sequence of events in the IFN-pyrin pathway will help us assess this hypothesis and contribute to understanding the puzzle of inflammation.

References:
14. Aypar E, Bakkaloglu A, Okur H, Besbas N, Kutluk T and Ozen S. Th1 polarization in FMF: What was the trade-off for the heterozygotes? Submitted for publication