Brief Report

A brief history of familial Mediterranean fever

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Although familial periodic fever syndromes were described and identified in the latter half of the twentieth century, there have been descriptions of periodic fever since antiquity. In this short historical study, these milestones are briefly described starting with Galen and ending with the characterisation of the Mediterranean FeVer (MEFV) gene towards the end of the twentieth century, and the elucidation of the involvement of the inflammasome in Pyrin action in the early years of the current century.

Familial Mediterranean fever (FMF) is the most common of the periodic fever syndromes. It is an inherited polyserositis that mainly affects Arabs, Armenians, Jews, and Turks. It is characterized by recurrent attacks of fever associated with joint, chest, and abdominal pain, and the appearance of an erysipeloid rash lasting 1-3 days. Treatment with colchicine is effective in preventing attacks and reducing the incidence of long-term complications such as amyloidosis.

Although familial periodic fever syndromes were only described in detail and identified as discrete entities after the second half of the twentieth century, there have been descriptions of periodic fevers since antiquity. Galen, for instance, described cyclic fevers that he attributed to the different moon phases as early as the second century AD.[1] However, description of the various symptoms and organ involvement appeared only in the literature over the past 200 years, where several prominent authors described a syndrome of recurrent attacks of fever, abdominal, and chest pain associated with joint symptoms as shall be described in the following paragraphs.

In the book published a year after his death entitled "Commentaries on the history and cure of diseases", Heberden wrote in 1802 "besides the pain, which are constantly felt, or rage at certain times, there are others which are regularly intermittent, the fits of which return periodically as those of an ague; such as I have known in the bowels, stomach, breasts, loins, arms, hips, though it be, but seldom that such parts suffer in days and recur for years at remarkably regular short intervals. At that time periodic such a manner".[2] Almost a century later, Osler in 1895[2] described 11 cases, which periodically presented with different visceral manifestations and various rashes. Five of those cases had joint pain. Some of those cases may well have been auto inflammatory in nature. In addition, Janeway & Mosenthal[4] in 1908 reported a young girl with intermittent fever and abdominal pain. The case was reported as "an unsolved diagnostic problem".[4]

Whether these descriptions refer to Familial Mediterranean Fever (FMF) per se, or some other familial periodic fever syndrome is not certain. It is likely that they refer to FMF, since it is the most common of all the periodic fever syndromes. In the case described by Janeway and Mosethal,[4] the short duration of fever perhaps points to FMF instead of any other autoinflammatory syndrome.

The first accurate description of FMF was published in 1945 by Siegal[5] who reported 10 cases of what he described as "at present little understood and often undiagnosed" under the name 'benign paroxysmal peritonitis'. The syndrome since then, appeared under several other names including, periodic peritonitis, familial recurring polyserositis, Cattan-Mamou disease, Siegal-Cattan-Namou syndrome, and periodic disease. The latter term was coined by Reimann[6] in 1948, who wrote "In naming them the adjectives periodic, cyclic, rhythmic, episodic, relapsing, paroxysmal, recurrent and intermittent are used interchangeably before the noun indicating the outstanding characteristic, as noted in the title and in the references".[6] Many other names appeared in the literature, including paroxysmal syndrome, Armenian disease, Periodic abdominalgia, La maladie périodique, La maladie dite périodique, La maladie de Siegal-Cattan-Mamou, La maladie périodique de Reimann, Periodic fever, Epanalepsie Mediterranéene and Recurrent polyserositis.[7]

In 1951, 2 French physicians, Cattan & Mamou, noticed the association of FMF with renal disease.[8] The occurrence of amyloidosis was reported 7 years later by Tuqan at the American University of Beirut in Lebanon.[9] The actual modern name "familial Mediterranean fever" was coined by Heller et al[10] in 1958, who emphasized the genetic nature of the disease. The exact etiology of the disease was unknown for a long time. However, the increased frequency in Arabs, Armenians, Jews, and Turks, and possible hereditary nature was noticed earlier.[11] It was not until 1997 that the gene causing FMF (MEFV gene) was finally identified by positional cloning by 2 separate groups, American and French, and was mapped to chromosome 16.[12,13] The gene product, a 781 amino acid protein, was named pyrin

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by the American group and marenostrin by the French group (Mare Nostrum: Latin for Mediterranean Sea). Since the identification of the MEFV gene in 1997, many studies, each involving up to a dozen or more investigators, were carried out by various groups around the world, all of whom broadened our understanding of this ancient disease at the molecular level. Listing each of these investigators is beyond the scope of this short historical study. To produce an inclusive list, one would have to include everyone who contributed to molecular biology since Watson and Crick and even beyond. However, I will briefly mention the most important advances.

The introduction of colchicine in 1972 as a prophylactic treatment in FMF has dramatically reduced the frequency of attacks as well as the incidence of the dreaded complication of amyloidosis. Despite its association with modernity, colchicine has been used for hundreds of years in an herbal form. In the early eleventh century Ibn Sina (Avicenna) described colchicum in the 'Canon of medicine' for the treatment of joint pains and gout.[14] Ibn Sina perhaps did not know at that time how colchicum worked in relieving joint pains, but he knew that it did work. Eight centuries after Ibn Sina described colchicum, French chemists Pierre-Joseph Pelletier and Joseph Bienaimé Caventou isolated colchicine from the autumn crocus *Colchicum autumnale*, after which it was named in 1820. However, it was not until 1972 that colchicine was used prophylactcally in FMF.[15] Two years later, in 1974, the efficacy of colchicine was established through randomized controlled trials.[16,17] In 1976,[18] previous trials reported that colchicine works by inhibiting leukocyte migration, one and a half centuries after it was isolated. The discovery of a caspase-activating complex by Martinon et al[19] in 2002, which they named "The Inflammasome", provided the groundwork for unravelling the precise molecular mechanisms whereby pyrin participates in the disease process.[19] Five years later in 2007, Papin et al[20] in Switzerland showed that pyrin binds several components of the inflammasome, particularly caspase-1 and interleukin-1ß. This was a breakthrough discovery that finally uncovered the precise disease process at the molecular level.

The discovery of MEFV gene and pyrin, marks a quantum leap in our understanding of nature of this interesting disease. Despite extensive study, the exact function of pyrin is not fully understood at present and the story of our understanding of the disease process and the potential institution of effective, and hopefully curative therapy, continues into the twenty-first century.

In conclusion, FMF is an ancient inherited periodic disease that had appeared in the literature under various names. Molecular characterization of the disease at the turn of the current century enormously expanded our understanding of the disease.

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References

1. Reimann HA. Periodic disease. ***Medicine*** 1951; 30: 3.
2. Heberden W. Commentaries on history and care of disease. London (UK): Wells and Lilly; 1802. p. 151.
3. Osler W. On the visceral manifestations of erythema multiforme. ***Am J Med Sci*** 1895; 110: 629.
4. Janeway TC, Mosenthal HO. An unusual paroxysmal syndrome, probably allied to recurrent vomiting, with a study of the nitrogen metabolism. ***Arch Intern Med*** 1908; 2: 214-225.
5. Siegal S. Benign paroxysmal peritonitis. ***Ann Intern Med*** 1945; 23: 1-21.
6. Reimann HA. Periodic disease. ***JAMA*** 1948; 136: 239-244.
7. Reimann HA. Perplexities of a periodic entity. ***JAMA*** 1964; 190: 241.
8. Cattan R, Mamou H. [14 Cases of periodic disease, 8 of which are complicated by kidney diseases]. ***Bull Mem Soc Med Hop Paris*** 1951; 67: 1104-1107.
9. Tuqan NA. Periodic disease: a clinicopathologic study. ***Ann Intern Med*** 1958; 49: 885-899.
10. Heller H, Sohar E, Sherf L. Familial Mediterranean fever. ***AMA Arch Intern Med*** 1958; 102: 50-71.
11. Daccak M. Periodic peritonitis, analysis of 19 cases. ***Diseases of the Colon & Rectum*** 1966; 9: 168-172.
12. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. The International FMF Consortium. ***Cell*** 1997; 90: 797-807.
13. French FMF Consortium. A candidate gene for familial Mediterranean fever. ***Nat Genet*** 1997; 17: 25-31.
14. Hartung EF. History of the use of colchicum and related Medicaments in gout. ***Ann Rheum Dis*** 1954; 13: 190-200.
15. Goldfinger SE. Colchicine for familial Mediterranean fever. ***N Engl J Med*** 1972; 287: 1302.
16. Goldstein RC, Schwabe AD. Prophylactic colchicine therapy in familial Mediterranean fever. A controlled, double-blind study. ***Ann Intern Med*** 1974; 81: 792-794.
17. 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; 291: 932-934.
18. Dinarello CA, Chusid MJ, Fauci AS, Gallin JI, Dale DC, Wolff SM. Effect of prophylactic colchicine therapy on leukocyte function in patients with familial Mediterranean fever. ***Arthritis Rheum*** 1976; 19: 618-622.
19. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. ***Mol Cell*** 2002; 10: 417-426.
20. Papin S, Cuenin S, Agostini L, Martinon F, Werner S, Beer HD, et al. The SPRY domain of Pyrin, mutated in familial Mediterranean fever patients, interacts with inflammasome components and inhibits proIL-1beta processing. ***Cell Death Differ*** 2007; 14: 1457-1466.