FAMILIAL MEDITERRANEAN FEVER: A PURINE METABOLISM DISORDER

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SUMMARY: Familial Mediterranean fever (FMF) is an inherited disorder characterized by fever, abdominal and/or chest pain. The etiology and pathogenesis of the disease remain unknown. A large amount of amorphous urate excretion in urine was found in five FMF patients during acute episodes. Increased excretion of uric acid in the patients with FMF during acute episodes can lead to the thesis that FMF is an inherited disorder of purine metabolism.

Key Words: FMF, purine metabolism, inherited disease.

INTRODUCTION

Familial Mediterranean Fever (FMF) is a heredofamilial disorder, characterized by recurrent episodes of fever, peritonitis and/or pleuritis. Arthritis and skin lesions may occur in some patients. It is usually restricted to people of Mediterranean ancestry (1-3, 5, 9-11, 14). Its etiology and pathogenesis remain unknown. Despite the striking features of fever and inflammation during acute attacks of FMF, to date no evidence of specific infectious agents have been identified (3,5,11,14). Similarly the suggestion that FMF may be mediated by an allergic or hypersensitive reaction was not documented (14).

A number of immunologic studies including examinations of the lymphocyte subpopulation and complement system as well as investigations concerning circulating immune complexes, immunoglobulins, lymphoctoxins and auto antibodies have failed to yield consistent results (3,5,9,11,12,14).

It has been reported that C5a-inhibitory deficiency (the complement-derived chemotactic anaphylatoxin) in joint and peritoneal fluids may have a role in the pathogenesis of the inflammatory attacks. How such a mechanism might account for exacerbations and remissions of recurrent polyserositis, is a question still not answered (8,13).

The demonstration that certain emotional or environmental changes may lead to the increased frequency of FMF attacks, has been proposed as a psycosomatic basis for this disorder. This theory also remains far from being acceptable to most authorities on the subject.

Unconjugated etiocholanolone blood levels were found elevated during the attacks in some patients. But further studies failed to reveal significant correlation between levels of etiocholanolone and FMF (3,11,14).

Excessive urinary excretion of porphirins in FMF on the other hand are likely to be examples of true porphyria and not FMF (11,14).

However, there is no evidence for a specific etiology of the disease (14).

Demonstration that FMF is inherited as an autosomal recessive disorder had led to the belief that it may be an inborn error or metabolism. However, no basic Biochemical defect has been identified in this disorder (1,4,11,14).

The etiopathology of FMF therefore still remains in complete darkness allowing further hypotheses. Thinking in these lines 1 observed large amounts of sodium urate in urine during acute attacks in five FMF patients. In these patients the increased urinary excretion of sodium urate started with acute attact at the same time. This characteristic feature of the urine continued throughout the acute attack, and remained at the maximum in the first 8-12 hours of the attack. These urines were pirkish in color and fairly cloudy. An excessive precipitate in these urine specimens were seen on standing. Their reactions were acid. The precipitate consisted of amorphous urate. After cen-

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trifugation of the urine, amorphous urate was also seen in the sediment. The characteristic of the urine returned to normal after resolution of the attack. This change of urine has been uncovered in numerous attacks observed in these 5 patients. Serum uric acid level however remained normal during acute attacks in these patients.

In humans, uric acid is the ultimate catabolite (end product) of purines. Reasoning from observations made in humans with inherited enzyme deficiencies, it appears that over 99% of the uric acid derived from substrates of purine nucleosid phosphorylase, a component of the purine salwage pathway. Sodium urate is a monosodium salt of uric acid (6,7).

The best known purine metabolism disorder is gout. This disease is mainly manifested by an increase in the uric acid level and recurrent attacks of acute arthritis. Colchicine is used effectively during the acute gout attack (6,7,14). It is well known that colchicine strikingly reduces the incidence of symptomatic febrile episodes, the mechanism of amelioration however remains unclear (3, 4, 11, 14).

Demonstration of large amounts of urates in urine present in FMF patients during acute attacks has led us to hypothesize that it may be a variant of inherited disorder of purine metabolism, which under other conditions may manifest itself as gout disease. While excessive production of urate was observed in FMF patients during acute attacks, questions about the nature and extent of the metabolic defect in purine metabolism responsible for FMF and its spontaneous resolution remain to be answered. Nevertheless it should be recalled that spontaneous resolution of the acute attacks are also seen in the gouty subjects (14).

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