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**Glomerular lesions other than amyloidosis in patients with familial Mediterranean fever**

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**Introduction**

Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease which primarily affects Jews, Armenians, Arabs and Turks [1,2]. The disease was first outlined by Siegal in 1945 and characterized by recurrent and self-limited attacks of fever, usually accompanied by peritonitis, pleuritis, arthritis or erysipelas-like erythema [3]. The development of amyloidosis is the most common renal complication of FMF that leads inevitably to chronic renal failure [4–7]. The frequency of amyloidosis differs among various ethnic groups and depends on whether patients are taking colchicine [1,2]. It has been well documented that the presence of amyloidosis determines the prognosis of the disease. However, in addition to amyloidosis other renal lesions have been described in the patients with FMF and it seems that these renal lesions have been relatively neglected [6–13].

**The spectrum of renal involvement other than amyloidosis in FMF**

Soon after the first well documented cases of FMF were published it became apparent that renal involvement is one of the most important features of the disease. The first identified renal lesion was amyloidosis in the patients with FMF who had persistent proteinuria [4]. In 1955, Shwayri and Tutunji [8] reported a case whereby a patient had abdominal and thoracic pain (FMF) with synchronous gross haematuria, but no tissue diagnosis was available. Furthermore, the occurrence of microscopic haematuria during attacks, but sometimes also in no relation to them, has been observed [5]. In 1970, Eliakim et al. analysed renal manifestations of 106 patients with FMF and found that 12.3% had amyloidosis, while 21.7% had renal lesions other than amyloidosis. Patients in the last category clinically presented with transient or persistent haematuria and albuminuria, particularly during attacks, and a variety of glomerulonephritides including acute post-streptococcal glomerulonephritis and Henoch–Schönlein purpura (HSP) were found. Histologically some of the kidney biopsies showed mesangial proliferation, but no immunofluorescence studies were performed [7]. In 1982, Flatau et al. showed focal mesangial proliferative glomerulonephritis in two patients who had FMF and HSP [13]. During the last decade more renal biopsies were performed in patients with FMF who had urinary findings. A variety of non-amyloid glomerular diseases were described. The presence of mesangial proliferation, IgM nephropathy, IgA nephropathy, focal and diffuse proliferative glomerulonephritis, mesangiocapillary...
glomerulonephritis, and rapidly progressive glomerulonephritis were reported in patients with FMF even in the absence of amyloidosis [6,9–12]. In addition, some of the non-amyloid glomerular lesions described in the patients with FMF were associated with vasculitis [6,7,12–14]. Furthermore, the coexistence of a variety of vasculitic syndromes with FMF was noted to be more frequent than in general population [13,14].

Possible pathogenesis

The biochemical basis of FMF is still unknown but the gene responsible for the disease was cloned recently by two independent teams [15,16]. The gene product called pyrin/marenostrin was reported to be a protein that is responsible for limiting the intensity of inflammation. It was suggested that FMF-associated mutations and the resultant structural changes of the protein interfere with the normal pyrin/marenostrin mediated negative feed back mechanism, thus favouring the onset and persistence of inflammation [15–17]. Although the identification of the FMF gene advanced the understanding of the regulation of acute inflammatory responses, the pathogenesis of the disease is still obscure. Based on clinical and laboratory findings several pathogenetic mechanisms have been suggested. Circulating immune complexes, complement consumption, increased concentrations of immunoglobulins during attacks and return to normal after the acute attacks support the notion that an immune reactant mechanism underlies FMF [6].

It is not known whether the presence of non-amyloid glomerular diseases with FMF is coincidental or causal. But a detailed review of the presentation, clinical course and histopathologic results of the reported cases in the literature favours a causal relationship. Although the exact pathogenesis of the development of non-amyloid glomerular lesions in the patients with FMF is unknown recent evidence suggests that an immunologic mechanism may play an important role in most of them, including acute post-streptococcal glomerulonephritis, type II rapidly progressive glomerulonephritis and IgA nephropathy [6,9,10]. In addition, Said and Hamzeh [11] suggested that the presence of mesangial IgA, IgM and C3 deposits that were observed in the patients with FMF and renal involvement may represent an immunoreactant mechanism. Another possible explanation is the entrapment of these substances as a result of mesangial dysfunction in clearing and processing immunologically-irrelevant macro-molecular aggregates. The frequent association of mesangial proliferation also offers good supportive evidence for an immunological process underlying the development of non-amyloid renal lesions in the patients with FMF. As FMF can be described as a disease of defective inhibition of inflammation, resulting from the mutations of the gene, it can be speculated that patients with FMF might have an exaggerated response to certain antigens that sometimes exceeds the clearing and processing capacity of the glomerulus and facilitates the development of these non-amyloid glomerular diseases.

Conclusion

The observations reported from different countries indicate that the patients with FMF are prone to exhibit a variety of glomerular diseases other than amyloidosis. Although amyloid renal disease is definitely common in FMF patients, there are no good epidemiological studies showing that non-amyloid glomerular diseases are also more frequent in the patients with FMF than in the general population. An important source of confusion is the interpretation of persistent albuminuria as a sign of amyloidosis in the absence of histologic proof. It is pertinent to point out that the actual frequency of non-amyloid glomerular lesions in patients with FMF depends largely on the number of kidney biopsies performed in patients with abnormal urinary findings. Colchicine treatment was clearly shown to ameliorate the course of FMF and to prevent the development of amyloidosis [1,2]. A review of the literature reveals that some of the FMF patients were not taking regular colchicine treatment when they developed non-amyloid glomerular diseases [5–12]. It remains to be seen whether regular colchicine treatment that prevents acute attacks and amyloidosis, may prevent the development of non-amyloid glomerular diseases in the patients with FMF. Finally, it is important to emphasize that non-amyloid glomerular diseases should be considered in the differential diagnosis of the patient with FMF and renal involvement.

References

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Does cyclosporin have a role in the treatment of membranous nephropathy?

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Introduction

Idiopathic membranous nephropathy (IMN) is an immune-mediated glomerular disease, usually associated with a nephrotic syndrome. The renal prognosis may be variable but a recent review of the available studies, including nongenetic and non-nephrotic patients, reported that renal survival at 10 years was 0.65 [1]. It is likely, however, that the prognosis is even worse in nephrotic patients, as the risk of renal failure is correlated to the severity and the duration of proteinuria [2]. Nephrotic patients are also exposed to an increased risk of cardiovascular death [3] as well as to intravascular thrombosis and other potential complications [4]. Thus, although many clinicians still adhere to the dogma that IMN should not be treated, it is our opinion that any treatment that is able to modify the natural course of this disease in patients with the nephrotic syndrome is welcome.

Treatment with corticosteroids and/or cytotoxic agents

Corticosteroids have been used in IMN for many years. A meta-analysis of the available controlled trials concluded that, at least at the doses used in the few available randomized trials, corticosteroids neither improve the probability of remission of proteinuria nor protect from renal function deterioration [1]. Controlled studies showed that the administration of cyclophosphamide or chlorambucil for 1 year or more may cause consistent reduction of proteinuria in a certain number of patients (see review in [4]) although admittedly prolonged treatment with alkylating agents theoretically exposes the patient to disquieting long-term side-effects.

The results of three multicentre trials made in Italy showed the effectiveness of a schedule based on alternating cycles of methylprednisolone and chlorambucil every other month for 6 months. A first study compared the effects of methylprednisolone and chlorambucil and those of symptomatic treatment in patients with IMN and nephrotic syndrome. At 10 years, 92% of treated patients versus 60% of untreated controls were still alive without dialysis. Treated patients spent 58% of their time without nephrotic syndrome versus 22% of controls [5]. A second study compared methylprednisolone and chlorambucil, and methylprednisolone alone given at the same cumulative dose. At the end of a mean follow-up of 54 months, 64% of patients given methylprednisolone and chlorambucil versus 38% of patients given methylprednisolone alone were without nephrotic syndrome, the difference being significant [6]. In a third trial methylprednisolone and chlorambucil were compared with methylprednisolone alternated with cyclophosphamide [7]. The probability of attaining as a first event complete or partial remission of the nephrotic syndrome was similar (82 vs 93%), the risk of relapse was also similar (30 vs 20%). Thus, the use of steroids alternated with either chlorambucil or cyclophosphamide may favour remission of the nephrotic syndrome and may protect renal function in the long term. It is worth remembering that in more than half of responders, remission of proteinuria develops weeks or months after the treatment was completed [5–7].

Results with cyclosporin

In the last few years cyclosporin has been used in a number of proteinuric glomerular diseases including...