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Review article

The spectrum of urological disease in familial Mediterranean fever: amyloidosis and beyond

Ahmad H. Hassan, Ghada A. Shousha*, Zeinab A. El-Sayed*
*Pediatric Nephrology Unit, *Pediatric Allergy, Immunology and Rheumatology Unit, Department of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt*

Introduction

Familial Mediterranean fever (FMF) is the most common inherited monogenic autoinflammatory disease that gained the attention of researchers for decades. Population from East Mediterranean origin are mainly affected**.**[1] Prevalence of FMF in endemic countries varies from 1:500 to 1:1,000; Turkey has the highest number of patients followed by Israel and Armenia**.**[2] The most commonly incriminated genotypes are recessive gain-of-function mutations of the Mediterranean fever (MEFV) gene. MEFV gene, M694V, was proved to carry greater risk of developing secondary amyloidosis, a potentially lethal complication. Authors claimed that environmental factors and country of origin might augment the risk of amyloidosis in infants and children with FMF.[3]

MEFV gene and pyrinopathy

MEFV gene, located on chromosome 16 (16p13.3), encodes a protein called pyrin which exists in several isoforms located both in cytoplasm and nucleus.[4] The main function of pyrin is regulation of the innate immune system. Pyrinopathies, the autoinflammatory disorders sharing the same immunopathogenesis as pyrin mutation, can deviate the innate immune cells towards unexplained activation.[3] Pyrin activation leads to oligomerization with other cellular proteins, forming a complex known as 'pyrin inflammasome'. This inflammasome, in turn, activates caspase-1 stimulating the pro-inflammatory cytokines (IL-1β and IL-18) and cause immature cellular apoptosis (pyroptosis) (figure 1).[5,6]

Over production of the pyrin inflammasome is responsible for the typical febrile inflammatory attacks (the classic phenotype) observed in FMF. The selective organ affection in FMF is explained by the presence of pyrin in innate immune cells such as granulocytes, monocytes, dendritic cells, and synovial as well as serosal fibroblasts.[1,7,8] The self-limited nature of FMF attacks is related to the simultaneous production of neutrophil extracellular traps (NETs) which involve a negative feedback mechanism, restricting further production of IL-1β.[9] IL-1β activation has a central role in the episodic systemic inflammatory manifestations in FMF such as serositis and neurological symptoms. In severe occasions associated with chronic inflammation, IL-1β might get involved in the tissue damage related secondary amyloidosis.[10]

The prevalence of renal involvement in FMF

The Turkish FMF study group reported a frequency of 12.9% of biopsy-proven amyloidosis (amyloid kidney disease, AKD), and only 0.8% of non-amyloid kidney disease (NAKD) among 2436 patients with FMF.[11] This is in contrast to the study by Kukuy et al in which 40% of FMF patients with proteinuria (n=25) had NAKD.[12] An Egyptian study conducted on 55 FMF patients reported amyloidosis in 27.3% (n=15) of patients.[13] Labib et al., have reported renal amyloidosis in 118/3962 renal biopsies (2.97%) examined for Egyptian patients of different ages, 73.7% of them had secondary amyloidosis and 40.6% of them suffered from FMF.[14] Similarly, according to the Theodor Bilharz Research Institute, Cairo, Egypt, 2.5% of renal biopsies showed amyloidosis, 80% with secondary amyloidosis and 30% of the latter group had FMF.[15] Unfortunately, data from Egyptian patients with FMF associated with renal affection are lacking.

The spectrum of urological disease in FMF

Acute urological presentations:

The fundamental (canonical) manifestations of the recurrent short-term self-limited inflammatory attacks of FMF are fever, serositis, arthritis and erysipelas like erythema.[1] Additional non-canonical manifestations were described, including neurologic, thrombo-embolic, and ocular symptoms.[16] Dysuria was among the described non-canonical manifestations that associate the short-lived attacks of FMF in children**.** It is one of the misleading symptoms, mistaken for urinary tract infection, appendicitis or other differential diagnoses of acute abdomen with dysuria, and thereby, delaying the

diagnosis of FMF.[17,18] Uncommon presentations included acute scrotal pain documented in limited articles.[19,20] Ureteric stones are another rare association.[21]

Long term urological complications:

Secondary renal amyloidosis complicating FMF is the result of amyloid A renal deposition and is responsible for up to 8.6% of rapid progression to end-stage renal disease, ESRD.[22] Proteinuria and eventual uremia are the main presenting symptoms of secondary amyloidosis.[23] Patients may initially present with amyloidosis (2%) rather than typical febrile attacks of FMF.[11] Risk factors implicated in the development of amyloidosis include M694V mutation, male gender, age of disease onset, and frequency of attacks[24,25] plus country of origin.[3]

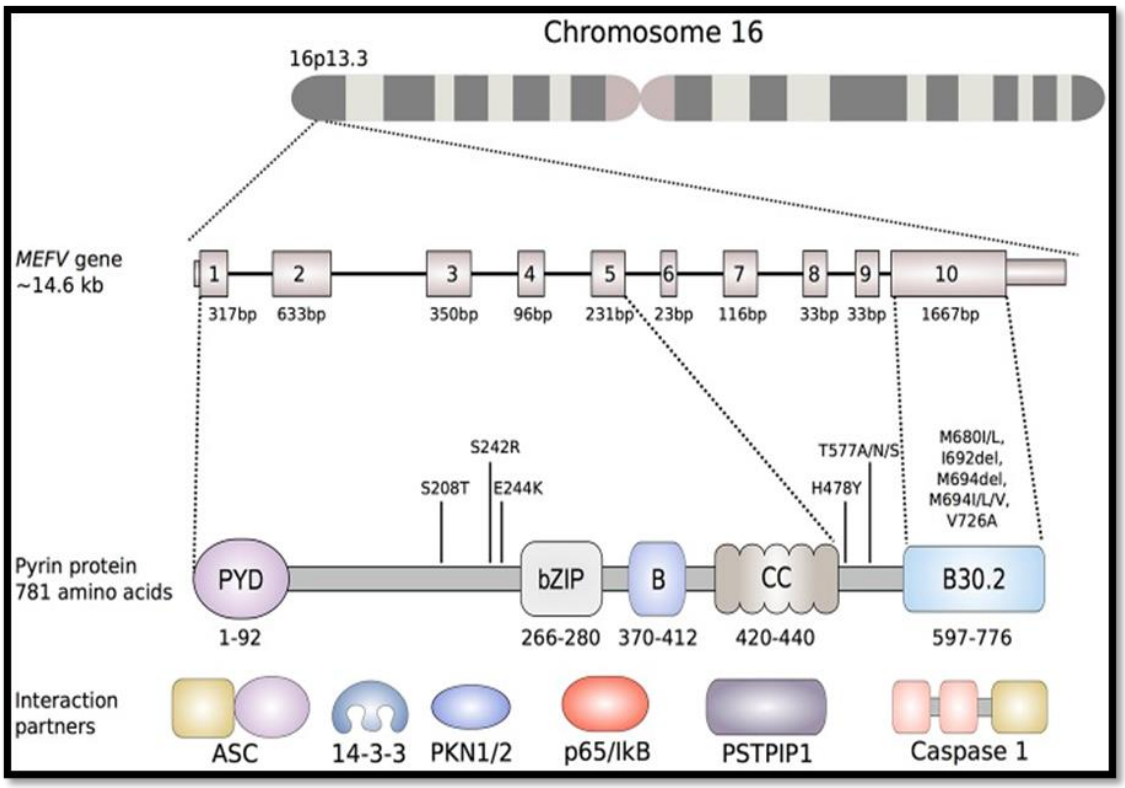

Figure 1. Schematic representation of the *MEFV* gene and the encoded pyrin protein.[5]

Secondary urinary bladder amyloidosis. This is an extremely rare complication. It was reported in a 64-year-old patient with FMF related amyloidosis after surviving from kidney transplantation. The presenting symptoms were persistent fever and fatigue followed after 6 months by macroscopic hematuria.[26]

Urological disease in relation to associated major histocompatibility complex class I diseases (MHC-I opathies). MHC-I opathies were repeatedly reported in association with FMF. Similar to FMF, MHC-I opathies share the same immunopathogenesis and hyper-stimulation of pro-inflammatory cytokines.[27,28] The urological manifestations may present in MHC- I opathies such as: Henoch Schönlein purpura (HSP), polyarteritis nodosa (PAN) and glomerulonephritis.[27,28,29]

Non-amyloid kidney disease (NAKD). There is an unexplained tendency in patients with FMF to develop glomerulonephritis and chronic kidney disease (CKD). The NAKD includes a heterogenous group of proteinuria causing mesangial IgA nephropathy, crescentic, rapidly progressing glomerulonephritis, diffuse proliferative glomerulonephritis, IgM nephropathy and vasculitis. They are mainly related to the uncontrolled inflammatory status in some FMF patients rather than being a genotype-phenotype variety.[30] Over-expressed pro-inflammatory cytokines in FMF proved to stimulate endothelial and leukocyte cells in the kidney, leading to excessive evolution of reactive oxygen species. This in turn causes disruption to the glomerular endothelial structure and activates the coagulation system.[31] Furthermore, the prolonged extensive inflammation in FMF would augment the

complement consumption during the attacks enhancing the glomerular damage.[32]

NAKD patients have less proteinuria and are less likely to develop ESRD compared to FMF related amyloidosis.[12,33] Hypertension usually develops earlier than proteinuria and in severe cases, symptom-free intervals become shorter, subclinical inflammation persists between attacks and response to colchicine may be limited. Kidney functions and proteinuria, are crucial to be monitored on regular basis in FMF patients.[34]

The cardiovascular-renal disease reciprocal perpetuation in FMF. FMF patients are at increased risk of atherogenesis and cardiovascular disorders, including hypertension and thrombo-embolic manifestations.[33,35] Decreased endothelial flow mediated diameter and increased carotid intima media thickness were proved in FMF patients, increasing the burden on kidneys.[36,37] On the other hand, renal amyloidosis was found to worsen the cardiovascular risk in FMF patients[38,39] and responsible for the worst prognosis among other etiologies of renal affection as regards the response to peritoneal dialysis[40] and post-transplantation morbidity and mortality.[41]

Predictors of renal and/or urological affection in patients with FMF.

1) *Urinary microalbumin (MA)* was widely accepted as the principle early predictor of FMF-related amyloidosis.[23] It is considered a marker of subclinical inflammation. MA/creatinine ratio is more sensitive than the rough estimation of urinary MA. Although mutations of MEFV gene, particularly homozygous M694V mutation, are associated with higher risk of amyloidosis,[23] in a case series, the different mutations were not correlated with urinary MA and urinary MA/creatinine ratio.[42]
2) *Serum amyloid A* levels are significantly correlated to the risk of mortality from amyloidosis.[43,44] It is considered a reliable indicator of subclinical inflammation and treatment adherence.[22]
3) *Mean platelet volume (MPV)* is a potential predictor of FMF-related proteinuria and amyloidosis. MPV is higher in children with proteinuria compared to their FMF peers without proteinuria. Generally, the volume is larger in FMF patients compared to healthy controls. Moreover, MPV is higher in adults compared to children with FMF. Therefore, it is thought that MPV combined with urinary MA might be more sensitive as predictors of amyloidosis in FMF patient.[45]
4) *Urinary neutrophil gelatinase-associated lipocalin (NGAL)* is an extracellular protein of the lipocalin family. Urinary NGAL is a diagnostic marker of glomerular and tubular dysfunction and an early predictor of acute kidney injury and CKD.[46,47] It was detected in higher levels in patients with FMF. Urinary NGAL/creatinine ratio was thought to be a more sensitive marker for FMF-related amyloidosis compared to urinary MA/creatinine ratio.[23]
5) *Urinary glycosaminoglycans (GAGs),* mucopolysaccharides found in the form of urinary unbound polysaccharides, are components of the glomerular basement membrane. They participate in the building structure of deposited renal amyloid, get consumed and their urinary levels become less detectable.[48]

Indications of renal biopsy

Persistent proteinuria higher than 500 mg/day, combined with incomplete response to treatment with colchicine may warrant the need for renal biopsy in the absence of contraindication.[34] Although it is not preferred in suspected renal amyloidosis, biopsy would help to determine if the proteinuria was related to amyloidosis (60% of patients) or to NAKD, as treating NAKD would include immunosuppressive agents.[49,50]

Renal amyloid prognostic score (RAPS)

RAPS was developed to standardize histopathological evaluation and grading of renal amyloidosis, a scoring and grading system which evaluates pattern and quantity of amyloid deposition in each compartment of kidney together with tubulointerstitial changes.[51] Renal survival in patients of FMF and amyloidosis can be predicted according to the RAPS grading. According to a recent study, only vascular amyloid load, but not glomerular amyloid and RAPS grade, was associated with poor renal outcome.[52]

Treatment of renal complications of FMF

Amyloidosis secondary to FMF, if diagnosed early, could follow regressive or, at least, stationary course when properly treated with colchicine.[42,53] Adjusted doses of colchicine should be considered in patients with impaired creatinine clearance. Close arterial blood pressure monitoring is mandatory in all patients with proteinuria. IL-1 inhibitors are needed for colchicine-resistant or intolerant patients, to control and improve the

proteinuria and impaired renal functions related to FMF amyloidosis.[54,55]

IL-6 inhibitor, Tocilizumab, was reported by authors to be of benefit in patients with colchicine resistant FMF associated with amyloidosis.[56,57,58] Role of tumor necrosis factor α (TNF- α) inhibitors, particularly infliximab[59,60] and adalimumab, in controlling AKD[61,62] and NAKD associating FMF was reported as well in some case reports and series. ESRD complicating FMF should be treated the same way as other causes of ESRD, including transplantation. Although amyloidosis has unfavorable prognosis after transplantation, NAKD induced ESRD has better prognosis.[41] Frequency rate of FMF associated amyloidosis among the waiting list for kidney transplantation was 8.4%.[63] However, precise control of inflammation through colchicine-adjusted doses or IL-1 inhibitors should be carefully maintained even in transplanted subjects.[27]

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