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Heterozygous MEFV Mutation Leading to Renal Failure: A Case Study

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Abstract

Familial Mediterranean fever (FMF) is an autosomal recessive disorder, particularly common in the Mediterranean area. Mutations in the *MEVF* gene cause it. AA Amyloidosis is the most severe complication of FMF leading to chronic renal failure. We describe a rare pediatric case of a phenotype I familial Mediterranean fever with *V726A* heterozygous mutation. The diagnosis was made at chronic kidney disease. We discuss through this case the importance of the early diagnosis of FMF heterozygous children which is not usually evident in some phenotypes. It will surely avoid fatal complications, inappropriate therapeutic approaches and higher healthcare costs.

Keywords

familial mediterranean fever, *MEFV* gene mutation, heterozygous, AA amyloidosis

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Introduction

Familial Mediterranean fever is an autosomal recessive inherited disease first described in 1957.[1,2]

It is particularly affecting Mediterranean-origin populations such as Arabs, Greeks, Italians, Armenians and Turks.[3]

FMF is defined by recurrent fever episodes associated to serositis (peritonitis, pleuritis, synovitis. . .). Amyloid protein accumulation leads to progressive systemic amyloidosis, which can cause renal failure.[4-6]

Three phenotypes of FMF have been reported :

Phenotype 1: clinical manifestations appear years before amyloidosis
Phenotype 2: amyloidosis first developed before any previous symptoms
Phenotype 3: asymptomatic homozygous or compound heterozygote state.[7,8]
FMF is due to a genetic mutation in the *MEFV* (for Mediterranean FeVer) gene, formed from 10 exons. The *MEFV* gene is situated on the short arm of chromosome 16, which codes for the pyrin protein or marenostrin.

MEFV expression in cells of myeloid lineage plays an important role in apoptosis and inflammatory response via interleukin (IL)-1β production. In fevers Database, 393 sequence variants of the *MEFV* have been identified. It's classified into five groups: namely, benign, likely benign, pathogenic, likely pathogenic and variants of uncertain significance (VUS).[9]

Colchicine is the gold standard treatment of FMF. Immunosuppressants are a second-line treatment for intolerant or resistant patients to colchicine.[10]

We report a pediatric familial Mediterranean fever with heterozygous mutation complicated by AA amyloidosis leading to renal failure.

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Case Report

A 9-year-old girl, born from a non-cansanguineous marriage complained 2 years before of recurrent fever and abdominal pain. She was admitted to our hospital at the stage of renal insufficiency.

Both parents and siblings were asymptomatic. Her physical examination was normal. Her weight and height were in the normal range.

Blood tests revealed white blood cell (WBC) counts 16 500/µl, hemoglobin was 9,2 g/dl, and platelet count was 536 000/µ.

Other laboratory parameters were as follows: serum urea nitrogen: 0,86 g/l, serum creatinine:4,52 mg/dl, total protein:34,32 g/l, albumin:13 g/l, Sodium:138 mmol/l, potassium 3,8 mmol/l, alkaline reserve <5, ferritin 201 ng/ml.

Erythrocyte sedimentation rate (ESR): 28 mm, C-reactive protein (CRP): 1,4 mg/l. Serum amyloid A (SAA) was normal tested after starting treatment. Proteinuria : 13 g/24 h (361 mg/kg/day). Serum C3 and C4 were normal. The serum level of IgG was $<1,08$ g/l, while IgA was 1,33 g/l and IgM was 0,4 g/l.

Immunological tests revealed that DNA anti-antibody, antinuclear antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor and Coombs test were negative.

Screening of hepatitis A virus, hepatitis B virus, hepatitis C, virus HIV, Cytomegalovirus, and Epstein-Barr virus were negative.

Trans Thoracic Echocardiography showed pericardial calcifications.

Abdomen and pelvic CT Scan described irregularly contoured kidneys with a small left kidney and mild pelvic fluid collection.

AA amyloidosis was diagnosed by renal biopsy containing 11 glomeruli :

Pale anhistic eosinophilic deposits on Hematoxylin-eosin staining with mesangial and parietal distribution. Interstitial fibrosis/tubular atrophy $<25\%$. Presence of identical segmental deposits in the walls of arterioles and interlobular arteries (Figures 1 and 2).

Congo red staining was used to validate the presence of amyloid deposits (Figure 3).

Immunohistochemistry: Glomerular deposits are SAA-positive.

Genetic analysis using Sanger sequencing on ABI 3500 (Thermo Fisher) showed the presence of the *MEFV* mutation (NM_000243):c.2177T>C (*p.Val726Ala*) in a heterozygous state in exon 10 of the *MEFV* gene. It's classified into a pathogenic variant. Exome sequencing wasn't done due to a lack of funding.

The patient was treated by daily subcutaneous injections of 3 mg/kg per day of recombinant IL-1 receptor antagonist (anakinra).

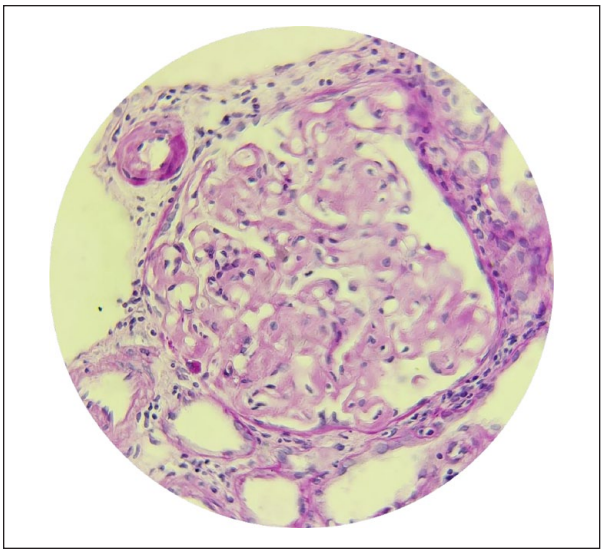

Figure 1. One glomerulus. Global distribution of pale eosinophilic amyloid deposits overflowing onto peripheral capillary walls. Segmental deposits in a juxtaglomerular arteriole. Hematoxylin-eosin staining, ×40.

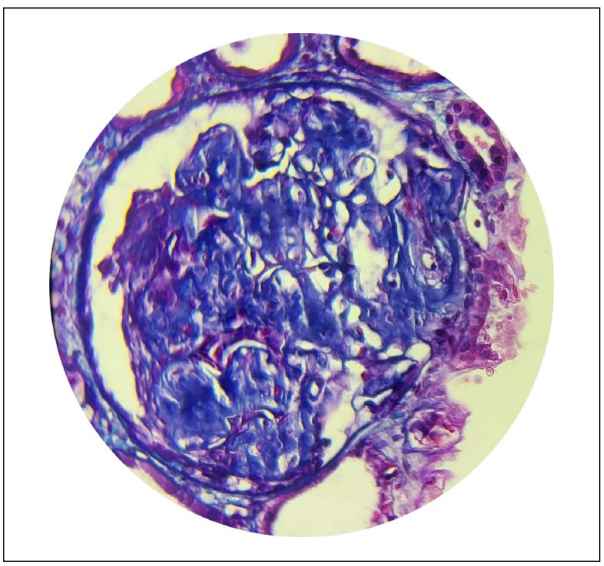

Figure 2. One glomerulus, abundant pale green nodular mesangial amyloid deposits on trichrome stain. Nile blue trichrome stain, ×40.

The evolution was marked by a decline in renal function at 3 months of follow-up. The patient was placed on automated peritoneal dialysis (APD).

Discussion

Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disease with autosomal recessive inheritance.[11] It has a notably high

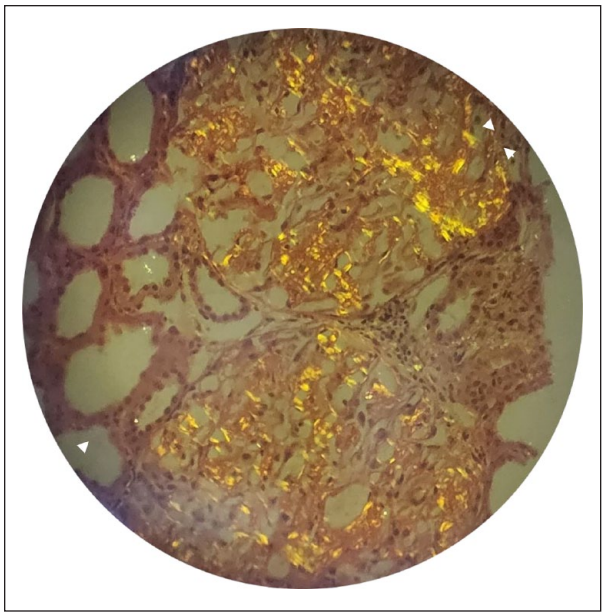

Figure 3. Two glomeruli. Amyloid deposits subjected to Congo Red staining and viewed under polarized light. Displayed yellow-green birefringence. Congo Red stain, ×20.

prevalence among populations of Mediterranean descent; however, FMF is being recognized in other regions of the world.

FMF results from mutations in the *MEFV* gene. It's situated on the short arm of chromosome 16 (16p 13.3) and is composed of 10 exons. *MEFV* gene encodes Pyrin/marenostrinis consisting of 781 amino acids. Pyrin/marenostrinis is a key regulator of inflammation mediated by IL-1b, which plays a critical role in the pathogenesis of FMF.

Sex is considered a non-genetic modifying risk factor in FMF-associated amyloidosis.[4] Male dominancy has been described in previous reports.[12,13]

According to Sohar et al,[7] 60% of 470 FMF cases were diagnosed in the first decade and 90% in the first two decades. Tunca et al[14] found that signs of 2838 cases started at the age of 9,6 years. The age of FMF diagnosis in Arab, Jewish and Armenian patients was respectively 80%, 67%, and 60% before the age of 10 years[7,14,15]

FMF diagnosis criteria require 2 major or 1 major + 2 minor criteria according to Tel Hashomer:

Major criteria:

- Recurrent fever attacks with serositis;
- AA amyloidosis, without other predisposing diseases;
- Symptoms responsive to colchicine

Minor criteria :

- Recurrent fever episodes;
- The presence of erysipelas-like erythema;
- Family history of FMF;

It's a pediatric case diagnosed with renal failure and renal amyloidosis secondary to FMF. It was not considered previously before her admission to our hospital leading to a delay in diagnosis and treatment.

The diagnosis was then perceived by renal biopsy and genetic study at the age of 9 years. Each region of the world is specified with a common type of mutation, but the five prevalent *MEFV* gene mutations are *M694V*, *M694I*, *M680I*, *V726A* and *E148Q*.

On one hand, studies in the Arab populations[16-21] conducted that *M694V* variant was identified as the predominant mutation, with a high prevalence of the *V726A* variant in Syria, Jordan, Palestine and Lebanon. In Morocco,[22] the frequencies of the most frequent allele *M694V* and *M694I* are respectively 49% and 37%. In a large pediatric Turkish cohort of 263 patients, *M694V* was the most frequent and severe mutation.[23] In a large pediatric Turkish cohort of 263 patients, *M694V* was the most common and severe mutation.[23] A retrospective analysis of 500 FMF Egyptian pediatric patients confirmed that the phenotype, clinical features, treatment response and prognosis are influenced by the genotype.[24]

On the other hand, the largest FMF cohort of referrals in Israel supported that the *p.Met694Val* variant was the most common followed by *p.Glu148Gln* and *p.Val726Ala* variants.[25] The allelic frequency of *p.Val726Ala* is 27,61% followed by *p.Met694Val* (19,4%) in a large cohort of Crypriot patients.[26]

The development of amyloidosis in FMF disease is hypothetically linked to *M694V* especially in homozygous patients.[27,28] However, many investigators didn't find a proof for this association.[29] *V726A* is related to a lower prevalence of amyloidosis because it may play a protective role against the development of the complication. Our patient was heterozygous for the *V726A* mutation.

The most fearsome renal manifestation is persistent or massive proteinuria, nephrotic syndrome ending in chronic renal failure. In addition, Amyloid A deposition may also affect the nervous, cardiovascular and gastrointestinal systems. Amyloidosis is incurable but it is avoidable by reducing inflammation.

Colchicine is effective in early diagnosis of FMF to prevent attacks and the progression of amyloidosis. It wasn't used for our patient because of GFR < 30 ml/

min/1,73.[30-32] New promising therapeutic strategies such as monoclonal antibodies:

IL-1 inhibitors anakinra and canakinumab, and anti-IL-6 tocilizumab may be used in resistance, intolerance colchicine treatment or AA amyloidosis and severe renal failure.

In a large pediatric cohort of 542 patients diagnosed with FMF, 6,1% received IL-1 therapy. All individuals with renal amyloidosis were treated with an anti-IL-1 inhibitor.

It was used together with colchicine in four patients with renal amyloidosis after kidney transplantation.[33] 26 Turkish patients with refractory received anti-IL-1 treatment.[34] Five had renal transplantation and two had systemic amyloidosis. Proteinuria was identified in all these patients, it was increased in one of them and stable in two of them.

Nevertheless, present studies are restricted and further data on FMF are needed to assess the efficacy and the tolerance of Anakinra in the short and long term especially in end-stage renal disease.

Conclusion

In conclusion, our patient is one of those rare pediatric cases of FMF with heterozygous mutation showing the complexity of FMF genetics. Further studies are needed to explore new and rare mutations to establish an accurate diagnosis at a very young age, especially in heterozygotes, to identify risk factors associated with the development of amyloidosis and therefore to provide an adequate therapeutic approach.

Authors Contribution

All authors contributed significantly to elaborate this scientific document :
The first author of each department: wrote the text.
The second, third and fourth: assisted at its elaboration.
The latest one set the diagnosis and additionally corrected it.

Declaration of Conflicting Interests

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Ethical Statement

No ethical rule has been broken and the manuscript is in accordance with hospital ethical committee.

Informed Consent

Written informed consent was obtained from the patient's legally authorized representative.

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