CHAPTER 15

FAMILIAL MEDITERRANEAN FEVER (E85.0)

Nazlı CAF[1]

REMEMBER

- Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease. The disease progresses more severely in homozygous individuals.
- Familial Mediterranean fever is inherited in an autosomal recessive pattern with incomplete penetration. However, about a third of patients may have a single pathogenic variant (monoallelic disease).
- Due to the MEFV (Mediterranean fever gene) mutation on the 16p13.3 chromosome, which is responsible for the synthesis of pyrins, NLRP3 is defectively inhibited, and IL-1 production is increased. Disease pathogenesis occurs via this pathway.
- The second most common mutation after M694V, which is the most common mutation in FMF, is the E148Q gene mutation in exon 2.
- FMF mainly affects people of Mediterranean descent. The disease particularly affects Turkish, Arab, Sephardic, and Armenian populations. The prevalence was reported as 1:500–1:2000 in endemic regions, and the highest prevalence was reported from Turkey. Turkey is followed by Israel, and Armenia in terms of the incidence of the disease.
- Symptoms of FMF begin before the age of 10 in 65% of patients, and before the age of 20 in 90% of them.

[1] MD., Basaksehir Cam and Sakura City Hospital, Dermatology Clinic, drnazlicaf@gmail.com

have infertility should be evaluated by a gynecologist.

Urology

- Sperm abnormalities are not uncommon in male patients with FMF, and are associated with both colchicine therapy, and inflammation due to uncontrolled disease. Since sperm motility (and thus egg penetration) is dependent on microtubular function, colchicine affects sperm activity.
- In studies, when biopsy samples were taken from testes of patients with FMF, significant maturation interruption, and germ cell aplasia were detected in spermatocytes with amyloid deposition in blood vessels. There may be a relationship between testicular amyloidosis, and secondary azoospermia.
- A routine spermiogram is recommended in young men with FMF who have renal or another organ amyloidosis. In addition, these patients should be offered sperm freezing for the risk of azoospermia development in the later stages of the disease. Patients should be directed to a urology specialist to be evaluated in these aspects.

Gastroenterology

- In the literature, an increase in the prevalence of inflammatory bowel diseases (IBD) (ulcerative colitis and Crohn's Disease) has been found in patients with FMF. Crohn's disease may occur more frequently in individuals with FMF. MEFV gene mutation, which is the main gene responsible for FMF, was found significantly more frequently in patients diagnosed with IBD. This may explain the risk between FMF and IBD.
- Patients with FMF have a higher risk of non-alcoholic fatty liver disease. The patients should be assessed by a gastroenterologist in case of any symptoms, signs, and/or clinical doubt.

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BÖLÜM 1

AİLESEL AKDENİZ ATEŞİ (E85.0)

Nazlı CAF[1]

HATIRLA

- Ailesel Akdeniz Ateşi (AAA) en sık görülen monogenik otoinflamatuvar hastalıktır. Homozigot bireylerde hastalık daha şiddetli seyreder.
- Ailesel Akdeniz ateşi (AAA), penetrasyonu tam olmayan otozomal resesif bir hastalıktır. Ancak hastaların yaklaşık üçte biri tek patojenik varyanta (monoalelik hastalık) sahip olabilir.
- 16p13.3 kromozom üzerinde bulunan ve pirinlerin sentezinden sorumlu olan MEFV (Mediterranean fever (=ailesel Akdeniz ateşi) geni) gen mutasyonuna bağlı olarak NLRP3'ün kusurlu inhibisyonu meydana gelir ve IL-1 üretimi artar. Hastalık patogenezi bu yolak ile oluşmaktadır.
- AAA'da en sık görülen mutasyon olan M694V'den sonra en yaygın ikinci mutasyon, ekson 2'deki E148Q gen mutasyonudur.
- AAA, esas olarak Akdeniz kökenli insanları tutar. Özellikle Türk, Arap, Sefarad ve Ermeni popülasyonlarını etkiler. Prevalans endemik bölgelerde 1:500–1:2000 olarak raporlanmıştır ve en yüksek prevalans Türkiye'den bildirilmiştir. Hastalık görülme sıklığında Türkiye'yi İsrail ve Ermenistan takip eder.
- Ailesel Akdeniz ateşi hastalarının %65'inin semptomları 10 yaşından önce, %90'ının ise 20 yaşından önce başlar.

[1] Dr., TC Sağlık Bakanlığı Çam ve Sakura Şehir Hastanesi, Dermatoloji Kliniği, drnazlicaf@gmail.com

- Yapılan çalışmalarda, AAA'lı hastaların testislerinden biyopsi örnekleri alındığında kan damarlarında amiloid birikimi olan spermatositlerde belirgin matürason bozukluğu ve eşey hücre aplazisi saptandığı bildirilmiştir. Testiküler amiloidoz ile sekonder azospermi arasında da ilişki olabilir.
- Renal veya diğer organ amiloidozu olan AAA'll genç erkeklerde rutin spermiyogram yapılması önerilmektedir. Ayrıca bu hastalara hastalığın ilerleyen dönemlerinde azospermi gelişme ihtimaline karşı sperm dondurma işlemi de önerilebilir. Hastalar bu yönlerden değerlendirilmek üzere üroloji uzmanına yönlendirilmelidir.

Gastroenteroloji

- Literatürde AAA'lı hastalarda inflamatuvar bağırsak hastalıkları (İBH) (=ülseratif kolit ve Crohn Hastalığı) prevalansında artış saptanmıştır. Crohn hastalığı AAA'lı bireylerde daha sık ortaya çıkabilir. AAA'dan sorumlu ana gen olan MEFV gen mutasyonu, İBH tanısı almış hastalarda anlamlı olarak daha sık bulunmuştur. Bu durum da AAA ile İBH arasındaki riski açıklayabilir.
- AAA'lı hastalarda alkole bağlı olmayan yağlı karaciğer hastalığı riski daha yüksektir. Semptom, bulgu ve/veya klinik şüphe durumunda hastaların gastroenteroloji uzmanı tarafından değerilendirilmesi önerilir.

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