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The Frequency of Familial Mediterranean Fever Related Amyloidosis in Renal Waiting List for Transplantation

Böbrek Nakli Bekleme Listesindeki Ailesel Akdeniz Ateşi Bağlantılı Amiloidoz Sıklığı

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Abstract

Objective: Our goal is to investigate the distribution of MEFV mutations in patients with renal amyloidosis who are in renal transplant waiting list which is prepared for transplantation.

Materials and Methods: FMF was diagnosed in 25 of the 297 patients between the years 2004 and 2008, who were involved in the study (15 male, 10 female; age 34±7.8). 5 out of 25 patients were transplanted, remaining were waiting for Tx. Biopsy results were amyloidosis and taken from renal (n:16), rectal (n:8) and duodenal (1).All of them were carrier of mutations in both pyrin alleles.The primer cause of chronic renal failure in our group was secondary AA amyloidosis. DNA was isolated from 25 whole blood samples. The NanoChip Molecular Biology Workstation (Nanogen) uses electronic microarrays for mutation detection. Exon 2,3,5 and 10 of pyrin gene genotypes were identified in the NanoChip.

Results: Genetic analysis of the patients demonstrated that each subject carries either homozygote or compound heterozygote mutations of the gene. The most common mutations were M694V, V726A, E148Q and M680I.

Conclusions: The clinic manifestation and complain of our patients were febrile and painful attacks such as in the abdomen, chest and joints due to inflammation of the peritoneum, pleura and synovial membrane. The major problem in FMF is the occurrence of amyloidosis that primarily affects the kidneys causing proteinuria and renal failure. Dialysis and renal transplantation can be treatment, but it is important to diagnose FMF at earliest stages. The percentage of FMF patients in our waiting list was 8.4%. Moreover, in our region FMF incidence is highly frequent, so FMF should be chased by genetically so as to prevent chronic renal failure due to amyloidosis.

Key Words: Amyloidosis, FMF, Kidney Transplantation

Özet

Amaç: Çalışmamızın amacı, böbrek nakli bekleme listemizdeki ailesel Akdeniz ateşi'ne (AAA) bağlı amiloidoz gelişmiş son dönem böbrek yetmezlikli hastaların sıklığı ve MEFV genindeki mutasyon dağılımını araştırmaktır.

Gereç ve Yöntem: 2004-2008 yılları arasında bekleme listesinde olan toplam 297 hastadan AAA tanısı almış olan ve biyopsi ile amiloidoz tespit edilmiş olan 25 (15 erkek, 10 kadın) hasta çalışmamıza dahil edildi. AAA olan hastaların 5'ine böbrek nakli yapıldı. Hastaların 16'sına renal, 8'ine rektal ve 1'ine duedonal biyopsi yapılarak amiloidoz geliştiği belirlenmiş. Yirmibeş hastanın periferik kanından DNA izole edildi. Vakalarımızın tümünde pyrin geninin her iki allelinde de mutasyon bulundu. Çalışmada pyrin geninin exon 2, 3, 5 ve 10 bölgelerindeki mutasyonların belirlenmesi için DNA analizörü NanoChip kullanıldı.

Bulgular: Yirmi beş hastanın herbiri için mutasyon analizi yapıldı. Her bir hastanın ya homozigot veya heterozigot MFEV gen mutasyonu taşıdığı bulundu. En sık görülen mutasyonların sırasıyla M694V, V726A, E148Q ve M680I olduğu tespit edildi.

Sonuç: AAA'nin yaygın olduğu bir bölgede bulunduğumuz dikkate alındığında, diyaliz ve böbrek nakli tedavi secenekleri olmasına rağmen AAA'nin erken teşhisi ve tedavisi önem arz etmektedir. Pyrin genindeki mutasyonlar ile amiloidoz güçlü bir ilişki göstermektedir.

Anahtar Kelimeler: Ailesel Akdeniz ateşi, Amiloidoz, Renal transplantasyon

Introduction

Familial Mediterranean fever (FMF) is an inherited disorder of an autosomal recessive trait. The major clinical finding of FMF is recurrent and self-limited attacks of fever. Severe abdominal, articular and/or chest pain due to inflammation of the peritoneum, synovia or pleura usually accompany these episodes. Between attacks, FMF patients are usually free of symptoms. The most important complication of FMF is progressive systemic amyloidosis, a situation leading to renal failure, which can be fatal [1-3].

The discovery in 1997 of the gene responsible for FMF (MFEV) has gone a long way towards understanding its molecular basis. FMF gene encodes a protein known as pyrin that is thought to modulate apopitosis and NF-KB activation. Now almost 70 mutations have been detected, most of them on exon 10. Six mutations were discovered on exon 2 and one or two mutations on each of exons 1, 3, 5, and 9. Colchicine treatment is effective in treating or aborting the acute recurrent exacerbations of the disease and in preventing the development of amyloidosis [4-7]. The aim of this study was to explore the magnitude of the FMF problem and to describe clinical phenotypic and genotypic profile in dialysis patients. It is also imperative to diagnose amyloidosis early enough to start the appropriate treatment and care.

Materials and Methods

Patient:

297 patients (195 male and 102 female) who are in the renal transplantation waiting list enrolled between 2004-2008 were examined for primer cause of renal failure. The clinical picture of 25 cases consist

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of painful and febrile attacks. The attacks were severe occurring in the abdomen, chest and joints, lasting from 24-72 hours. The history of attacks were mainly starting during childhood or adolescence. The laboratory findings of patients were elevated sedimentation rate, high acute phase reactant titres (CRP), increased serum amyloid A (SAA) and fibrinogen. These subjects were undergone biopsy for examining 25 amyloidosis taken from renal, rectal or duodenal. Amyloid deposition was obtained in 25 biopsies. Biopsy amyloidosis proven cases were analyzed for MEFV mutations. Human genomic DNA was obtained by extraction in the MagNa Pure LC System (Roch Applied Science) from 25 whole blood samples.

NanoChip Assay:

Oligonucleotids, primers, and probes used in the NanoChip assay were provided by Nanogen (San Diego, CA). The PCR for exon 2, 3, 5 and 10 of MEFV mutations were performed according to instructions in the Nanogen FMF Application note.

Main goal of the study is to assess phenotype-genotype correlations in FMF, specifically, the role of MEFV mutations for amyloidosis occurrence.

Results

The clinic feature of patients with amyloidosis has been presented in Table 1.

The ratio of females to males is 0.6 (6:10) in patients with renal amyloidosis and is 0.8 (4:5) in patients with non renal amyloidosis. Consanguinity was documented in 4 of 25 (16%) of the patients. In our study population, most of the biopsies were taken from kidney. The remaining biopsies were not taken from the renal, so we do not know if the kidney has amyloidosis or not. Non renal amyloid deposition (rectum, duodenal) was present in renal chronic kidney disease patients. Here the question is if the primer of the disease is the different in non renal amyloidosis.

Discussion

In this study, we evaluated amyloidosis related renal failure patients rate within the renal transplantation waiting list and genotypes of patients. There are reports that FMF incidence is high in Turkey [8, 9]. In the study, 8.41% of waiting list appeared to be FMF patients. Abdominal pain attacks are the most common symptom and we believe that if the attacks are frequent, there is most probable amyloidosis leading to renal failure. It is, therefore, important to diagnosis of the disease as early as possible before amyloidosis initiating. Our series (FMF cases in renal waiting list) at this moment is not large, so it is difficult to make evaluation between genotype of patients and amyloidosis. There is regional study performed on pediatric group reported that M694V mutation is the most common one [10].

It has been known that the onset of the FMF occurs before age of 30. The relation between renal failure and FMF is the occurrence of amyloidosis. Kidneys are seriously affected by amyloidosis causing proteinuria and resulting in renal failure. Dialysis and transplantation are choice of the treatments. Colchicine can prevent amyloidosis, it is, therefore imperative in the care of FMF patients to diagnose amyloid deposition early enough to begin treatment.

Many studies have investigated various parameters for the risk of amyloidosis. Although there is no consensual conclusion, the chief risk factor for renal amyloidosis in FMF is the pyrine gene mutations. In our study all cases caries either homozygote or compound heterozygote mutations of the gene. It appears indisputable that a given allele combinations at the gene locus contribute to manifestations of the disease, notably, amyloidosis. Our results have quite important ramifications from a practical point of view. The importance of the diagnosis and treatment of FMF in patients with overt disease living in region where the disease is identified as high risk brings serious responsibilities such as initiating prophylactic treatment with colchicine to asymptomatic individuals who are incidentally discovered to be pyrine gene mutations.

It should be considered that the FMF Patients in this study had a different mutation combination, which could display intercultural interactions and these mutations seem to be not different in respect to clinical presentation.

Table 1. Distribution of the pyrin gene mutations in chronic kidney disease patients with amyloidosis

	Renal amyloidosis (n:16)	Non-renal amyloidosis (n:9)
Sex ratio(F/M)	6/10	4/5
Consanguinity	1/3	0/1
MEFV genotype		
M694V/M694V	5	1
M694V/M680I	1	1
M694V/V726A	1	1
M694V/E148Q	5	3
M694V/R761H	1	1
M694V/M694I	2	-
V726A/M680I	1	2
Colchicine	6/10	4/5

Conflict of interest statement The authors declare that they have no conflict of interest to the publication of this article.

References

1. Fonnesu C, Cerquaglia C, Giovinale M, et al. Familial Mediterranean Fever: A review for clinical management. Joint Bone Spine 2008: 1-7.
2. Ozen F. Familial Mediterranean Fever. Rheumatol Int 2006; 26: 489-96.
3. Hatem I. El Shanti. Familial Mediterranean Fever and Renal Disease. Saudi J Kidney Dis Transplant 2003; 14: 378-85.
4. Toutiou I, Sarkisian T, Medlej-Hashim M, et al. Country as the Primary Risk Factor for Renal Amyloidosis in Familial Mediterranean Fever. Arthritis & Rheumatism 2007; 56: 1706-12
5. Tunca M, Akar S, Onen F, et al. Familial Mediterranean Fever (FMF) in Turkey: result of a nationwide multicenter study. Medicine (Baltimore) 2005; 84: 1-11.
6. Akar N, Hasipek M, Akar E, et al. Serum amyloid A1 and tumor necrosis factor-alpha alleles in Turkish familial Mediterrean fever patients with and without amyloidosis Amyloid 2003; 10: 12-6.
7. Moser C, Pohl G , Haslinger I, et al. Successful treatment of familial Mediterranean fever with Anakinra and outcome after renal transplantation. Nephrol Dial Transplant 2009; 24: 676-8.
8. Odabas AR, Cetinkaya, Selcuk Y, et al. Familial Mediterranean Fever. South Med. J. 2002; 95: 1400-3
9. Ozdemir AL, Sokmen C. Familial Mediterranean Fever among the Turkisk people. Am. J. Gastroenterol. 1969; 51: 311-6.
10. Ertekin V, Selimoglu MA, Pirim İ. Familial Mediterranean Fever in a childhood population in eastern Turkey. Pedatr Int.2005; 47: 640-4