



Coexistence of Two Rare Genetic Disorders: Familial Mediterranean Fever and Neurofibromatosis Type 1 in a Child

İki Nadir Görülen Hastalığın Birlikteliği: Bir Çocukta Ailevi Akdeniz Ateşi ve Nörofibromatozis Tip 1

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ABSTRACT

Familial Mediterranean fever (FMF) is an autosomal recessive polysystemic disease characterized by attacks of relapsing and self-limiting fever, peritonitis, pleuritis and arthritis. Café-au lait macules, neurofibromas, axillary and inguinal freckling, Lisch nodules, bone lesions such as sphenoid dysplasia, and optic glioma are the characteristic features of neurofibromatosis type 1 (NF1) disease. In this case report, a 7 year-old girl with NF1 and FMF is presented. She had intermittent fever, abdominal and joint pain attacks lasting 2-3 days every two-three months since 1 year. We detected many cafe-au lait spots and axillary freckles on her body and diagnosed FMF and NF1.

Key words: Familial Mediterranean fever, neurofibromatosis type 1, coexistence.

ÖZET

Ailevi Akdeniz Ateşi (FMF) nökseden ve kendini sınırlayan ateş, peritonit, plörit ve artrit atakları ile karakterize otozomal resesif geçişli polisistemik bir hastalıktır. Nörofibromatozis tip 1 (NF1) hastalığının karakteristik özellikleri arasında café-au lait lekeler, nörofibromlar, aksiller ve inguinal çillenme, Lisch nodülleri, sfenoid displazi gibi kemik lezyonları ve optik gliom yer alır. Bu makalede, FMF ve NF1'li 7 yaşındaki bir kız sunulmuştur. Hastanın bir yıldır, 2-3 ayda bir 2-3 gün süren ateş, karın ve eklem ağrılarına sahipti. Bunun dışında vücudunda café-au lait lekesi ve aksiller çillenme saptadı ve hastaya FMF ve NF1 tanısını koyduk.

Anahtar kelimeler: Ailevi Akdeniz Ateşi, nörofibromatozis tip 1, bir arada olma

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common auto-inflammatory disorder seen in Middle East and Mediterranean region. FMF is inherited autosomal recessively and characterized by recurrent attacks of fever with peritonitis, pleuritis, arthritis, or erysipela-like skin lesions¹.

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder characterized by café-au lait spots, skin fold freckles, Lisch nodules, cutaneous, subcutaneous, and plexiform neurofibromas, optic gliomas, and bony lesions². It is well known that FMF may coexist with vasculitic disorders³⁻⁵. But, coexistence of NF1 and other disorders are

extremely rare. To date, there are only a few reliable reports of concomitant diagnosis of NF1 and other diseases such as Wilson disease, Alport syndrome, Mayer-Rokitansky-Kuster-Hauser syndrome, and Marfan's syndrome⁶⁻⁹. It is known that patients with NF type 1 also have predisposition to malignant diseases. We represent a rare case of a child with FMF and NF1. To our knowledge, this is the first report of coexistence of these rare genetic diseases in the literature.

CASE

A 7-year-old girl was admitted to the hospital with intermittent fever, abdominal and joint pain attacks lasting 2-3 days every two-three months since 1 year. Her mother and father were first-degree cousins, and her older sister was diagnosed with FMF. She has no family history of NF 1 disease.

On her examination, the vital signs, including the blood pressure were normal. Her height and weight were normal for her age. Many cafe-au-lait spots and axillary freckles were found on her body. There were no subcutaneous neurofibromas. Ophthalmic examination was normal. The remaining of the physical and neurological examination was unremarkable.

Laboratory studies including, liver and kidney function tests were normal. Erythrocyte sedimentation rate and fibrinogen were 42 mm/h (0-20 mm/h), and 320 mg/dl (200-400 mg/dl), respectively. Abdominal ultrasonography was normal. The patient's symptoms, signs, clinical and laboratory findings were consistent with FMF. DNA analysis revealed a heterozygous mutation on exon 2 of the MEFV gene (E148Q G>C), confirming the diagnosis.

Colchicine 1.5 g/day was started. NF1 was also diagnosed by clinical findings. But, genetic study could not perform.

DISCUSSION

The FMF is an inherited multi-system disease with recurrent painful attacks affecting the abdomen, chest or joints, and is often accompanied by fever and sometimes skin rash¹. It is an autosomal recessive disease and the gene responsible for FMF, MEFV, is located on the short arm of chromosome 16 and encodes a protein, pyrin or marenostrin^{1,3,10}. The most common four mutations, M694V, V726A, M680I, M694I are found in the 10th exon of the gene. A non-founder mutation, E148Q is found in populations in which FMF is rare. E148Q mutation located in exon 2 is also common¹⁰.

The prevalence of NF1 is 1/3000 live births. NF1 is an autosomal dominant disease, with approximately 50% of cases exhibiting new mutations. The gene involved in NF1 is located in the 17q11.2 chromosome and codes the protein neurofibromin².

Coexistence of NF1 with Wilson disease, Alport syndrome, Mayer-Rokitansky-Kuster-Hauser syndrome, Marfan's syndrome, and vitiligo universalis were reported in the literature⁶⁻⁹. In the literature no relationship was shown these diseases and NF 1. The authors suggested it was a coexistence. To our knowledge, this is the first report regarding its coexistence with FMF.

This patient presented with cafe-au-lait spots and axillary freckling. According to clinical criteria, she fulfilled the criteria of NF1, but had no positive family history. Diagnosis of NF1 is based on clinical criteria, although genetic study can be used for finding the mutations². Considering the clinical symptoms, increased frequency of FMF in our area, and the existence of FMF in her sister, our patient was evaluated for FMF. After determination of mutation in FMF gene, she was diagnosed for FMF.

Although coexistence of FMF with NF1 has not been published before, it was shown with HSP,

Behcet' disease, and juvenile idiopathic arthritis³⁻⁵. The overall incidence of vasculitis in FMF patients is 1% of PAN and 5% of HSP, and it is significantly higher in FMF patients than in normal population. Although exact pathogenesis of FMF-associated vasculitis remains unknown, increased serum levels of proinflammatory cytokines, including IL-1b, IL-6, IL-18, IL-33 and INF-c, and the resultant ECD seem to be important in vasculitis development in FMF patients^{11,12}. Among those cytokines, IL-1b is the most prominent one, and extremely high IL-1b activity may favor vasculitis development in FMF patients. FMF-related MEFV gene mutations contribute to vasculitis development at least in some FMF patients, possibly by means of causing higher levels of proinflammatory cytokines¹². The contributing effects of environmental factors, especially the streptococcal infections, also seem to be important¹³. We believe that our current knowledge regarding FMF-vasculitis pathogenesis is just the tip of the iceberg, and we need more data to uncover the facts underlying this association.

The pathogenetic relationship of NF1 and FMF is not clear. We could not establish a certain genetic relation between these two diseases but we suggest that the underlying genetic events may cause the pathology.

In conclusion, NF1 and FMF, which are two separate morbidities may also coexist in the same patient and our patient is the first example of FMF and NF1 coexistence in the literature. No genetic similarities between NF1 and FMF syndrome have been observed. As the two gene loci are not related, it is most likely that two independent mutation events have occurred. More extensive reports and further investigations of this combination will certainly provide a better understanding of this linkage in the near future.

REFERENCES

1. Ben-Chetrit E, Levy M. Familial Mediterranean fever. *Lancet*. 1998;351:659-64.
2. Upadhyaya M, Shaw DJ, Harper PS. Molecular basis of neurofibromatosis type I (NF1): mutation analysis and polymorphisms in the NF1 gene. *Hum Mutat*. 1994;4:83-101.
3. Ozkaya O, Bek K, Alaca N, Ceyhan M, Açıköz Y, Taşdemir HA. Cerebral vasculitis in a child with Henoch-Schönlein purpura and familial Mediterranean fever. *Clin Rheumatol*. 2007;26:1729-32.
4. Bakkaloğlu SA, Muzaç S, Akpek S, Söylemezoğlu O, Buyan N, Hasanoğlu E. Polyarteritis nodosa in a case of familial Mediterranean fever. *Pediatr Nephrol*. 2004;19:536-8.
5. Migita K, Abiru S, Sasaki O, Miyashita T, Izumi Y, Nishino A, et al. Coexistence of familial Mediterranean fever and rheumatoid arthritis. *Mod Rheumatol*. 2014;24:212-6.
6. Sahraian MA, Motamedi M, Paknejad SM, Azimi AR. Coexistence of Wilson's disease and neurofibromatosis type 1 in a 14-year-old boy. *Neuro India*. 2007;55:89-90.
7. Yaylı S, Bahadır S, Cimşit G, Bozkaya H, İmamoğlu Hİ, Kul S. Coexistence of Mayer-Rokitansky-Kuster-Hauser syndrome and neurofibromatosis type I. *Am J Clin Dermatol*. 2008;9:57-60.
8. Ding J, Yang JY, Yao Y, Liu JC, Li YB, Yu LX. Alport syndrome with neurofibromatosis type-I: a case report. *Pediatr Nephrol*. 1997;11:649-50.
9. Hartlapp I, Bühring U, Dichgans J, Isenmann S. A patient with Marfan's syndrome and neurofibromatosis type 1 with polyneuropathy. *Eur J Neurol*. 2004;11:641-4.
10. The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell*. 1997;90:797-807.
11. Tekin M, Yalcinkaya F, Tümer N, Akar N, Misirlioğlu M, Cakar N. Clinical, laboratory and molecular characteristics of children with familial Mediterranean fever-associated vasculitis. *Acta Paediatr*. 2000;89:177-82.
12. Simsek I, Pay S, Pekel A, Dinc A, Musabak U, Erdem H, et al. Serum proinflammatory cytokines directing T helper 1 polarization in patients with

familial Mediterranean fever. Rheumatol Int 2007;27:807-11.

13. Ozen S. Mutations/polymorphisms in a monogenetic autoinflammatory disease may be susceptibility

markers for certain rheumatic diseases: lessons from the bedside for the benchside. Clin Exp Rheumatol 2009;53:29-31.

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