

## Alpha thalassemia in a Symptomatic Carrier of Familial Mediterranean Fever

### Semptomatik Ailevi Akdeniz Ateşi Taşıyıcısı Bir Olguda Alfa Talasemi

Deniz Aslan

Section of Hematology, Department of Pediatrics, Faculty of Medicine, Gazi University, Ankara, Turkey

#### ABSTRACT

Alpha thalassemia and Familial Mediterranean Fever (FMF) are two diseases that affect the same societies native to the Mediterranean basin and have overlapping genetic localizations. Deletions resulting in alpha thalassemia have the potential to affect the neighboring MEFV gene (MEFV) and to lead to symptoms in FMF carriers. We herein present a symptomatic FMF carrier with coexistence of these two genetic diseases. This report may provide a simple explanation for an age-old mystery of how FMF can occur with a single mutation.

**Key Words:** Alpha thalassemia, deletion, Familial Mediterranean Fever, single mutation, symptom

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#### ÖZET

Alfa talasemi ve Ailevi Akdeniz Ateşi (Familial Mediterranean Fever, FMF) aynı coğrafik bölgede yerleşik toplulukları etkileyen ve genetik lokalizasyonu örtüşen iki hastalıktır. Alfa talasemiye yol açan delesyonların komşu yerleşimli FMF genini (MEFV) etkileme ve tek gen mutasyonlu FMF taşıyıcılarında klinik semptomlara yol açma potansiyeli vardır. Bu yazıda, bu hipotezi destekler şekilde, alfa talasemi taşıyıcılığı bulunan ve semptomatik olan bir FMF taşıyıcısı olgu sunulmaktadır. Bu yazı bilim dünyasını uzun zamandır meşgul eden 'tek gen mutasyonu ile FMF semptomları nasıl gelişebilir?' sorusuna verilecek yanıtlardan biri olabilir.

**Anahtar Sözcükler:** Alfa talasemi, delesyon, Ailevi Akdeniz Ateşi, MEFV, tek gen mutasyonu, semptom

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#### INTRODUCTION

It has been brought forward recently that one of the explanations for symptomatic Familial Mediterranean Fever (FMF) with only one mutation might be concomitant alpha ( $\alpha$ ) thalassemia (1). The overlapping genetic localization of these two diseases affecting the same populations was emphasized, and it was suggested that  $\alpha$ -globin gene deletions might affect the neighboring MEFV gene (MEFV) by several mechanisms. Other interested groups with advanced genetical laboratory facilities are studying this hypothesis in large patient populations. We herein present a clinical observation that supports the hypothesis they are testing, which we hope will encourage them in their ongoing studies. The case inherited one disease from each parent, and is unique with respect to this particular feature.

#### CASE REPORT

The patient was a 15-year-old Turkish male assessed for leukopenia. His personal history revealed that he suffered from abdominal pain and fever starting three days before that had resolved in two days. His medical records revealed that he had experienced repeated episodes of severe abdominal pain (usually accompanied with fever, chill, nausea, and fatigue) of unknown origin and was observed in the emergency room with a clinical suspicion for appendicitis. During the attacks of acute abdomen he had leukopenia (WBC 2.500 to 3.000  $\times 10^9/l$ ) instead of leukocytosis. Each episode of the attack continued for several days (1 to 4 days), and with the disappearance of the attack, the WBC count rose to normal level. All infectious causes were excluded by clinical and laboratory examinations.

**Address for Correspondence / Yazışma Adresi:** Deniz Aslan, Section of Hematology, Department of Pediatrics, Faculty of Medicine, Gazi University, Ankara, Turkey, Tel: 90-312-2026020  
E-mail: daslan@gazi.edu.tr

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The maternal uncle of the patient had thalassemia minor and had suffered from periodic episodes of fever and abdominal pain since childhood. In addition, the maternal grandfather had thalassemia minor. Results of the patient's hematological tests were consistent with  $\alpha$  thalassemia. The clinical course and high acute phase reactants suggested FMF. Mutation analysis revealed that he was heterozygous for the FMF mutation of V726A. In the core family investigation, the patient's mother was  $\alpha/\beta$  double heterozygote and the father was heterozygous for the FMF mutation of V726A. Results of the core family's hematological tests and their interpretations are shown in Table 1. Pedigree from the extended family showing the coexistence of thalassemia and FMF is presented in Figure 1. Leukopenia resolved on the third day after admission.

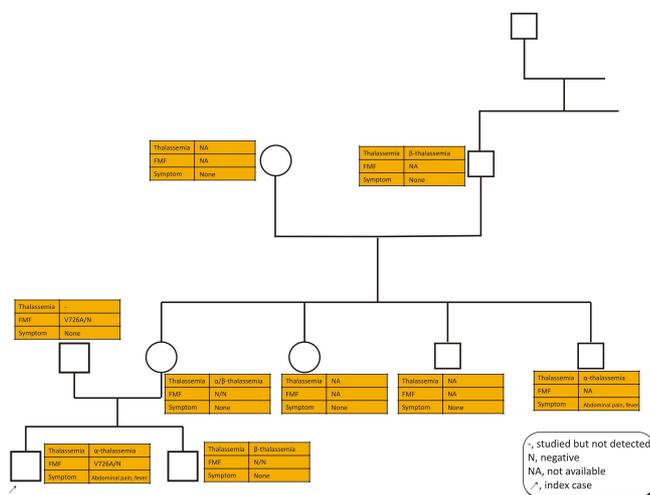
**DISCUSSION**

Alpha ( $\alpha$ ) thalassemia is a genetic hemoglobin disorder characterized by a microcytic hypochromic anemia (2,3). It is one of the most common of all human genetic disorders and is frequent in Mediterranean countries. In normal individuals,  $\alpha$ -globin synthesis is regulated by four  $\alpha$ -globin genes, two on each copy of chromosome 16 on band 16p13.3.  $\alpha$  thalassemia most commonly results from deletions in one or more of the four  $\alpha$ -globin genes. The clinical phenotype varies from almost asymptomatic to a lethal hemolytic anemia according to the number of deleted copies of the genes. FMF is also a recessive genetic disorder that affects the same populations of the Mediterranean basin and is caused by mutations in the MEFV gene (*MEFV*), which is also located at the 16p13.3 position (4).

**Table 1.** Hematological test results of the case and the core family members.

	Patient	Younger brother	Mother	Father
Hb, g/dl	13.4	9.9	10.0	15.3
MCV, fl	83.1	60.1	62.1	92.8
MCH, pg	28.6	20.4	20.5	32.3
MCHC, g/dl	34.4	34	32.9	34.8
RBC, x 10 <sup>12</sup> /l	4.7	4.8	4.9	4.7
Serum iron, $\mu$ g/dl	-	53	53	79
IBC, $\mu$ g/dl	-	270	316	318
Serum ferritin, ng/ml	-	17.7	10.1	95
Hb F, %	1.5	5.7	3.5	0.1
Hb A2, %	1.3	5.5	5.3	2.6
HbH inclusion bodies	(+)	-	-	-

**Interpretation of hematological tests.** Hematological test results in the patient are consistent with  $\alpha$  thalassemia with the combination of abnormal Hb analysis and demonstrable HbH inclusion bodies. The sibling, on the other hand, has  $\beta$  thalassemia in heterozygous form with the combination of severely reduced red cell indices with normal iron study results and elevated Hb A2 level. In the mother with two biological children, from the same male with normal hematological findings, having different types of thalassemias, a diagnosis of double heterozygosity should be considered. The incidence of double heterozygosity for different types of thalassemias is high in populations where thalassemia is frequent and the most common form of this situation is the combining heterozygosity for  $\beta$  thalassemia and  $\alpha$  thalassemia (11). As is known,  $\alpha$  thalassemia carried by  $\beta$  thalassemia heterozygotes is deletional type (12) and red cell parameters in  $\beta$  thalassemia heterozygotes combining deletional  $\alpha$  thalassemia are found to be similar to those in pure  $\beta$  thalassemia (13), as also observed in the mother.



**Figure 1.** Pedigree from the extended family showing the coexistence of thalassemia and Familial Mediterranean fever.

The MEFV gene encodes a protein called pyrin, an important modulator of innate immunity. Molecular aberrations affecting the MEFV gene dysregulate gene expression. In this situation, pyrin cannot be properly synthesized. Improper protein alters the inflammasome function and disrupts the regulation of inflammation, and the characteristic inflammatory symptoms seen in FMF develop subsequently. As well as the point mutations (identified or yet-to-be identified) affecting the ten coding exons of the MEFV gene, deletions removing the neighboring  $\alpha$ -globin genes and leading to  $\alpha$  thalassemia may affect the MEFV gene and may disrupt the synthesis of pyrin. For example, some of the deletions that result in  $\alpha$  thalassemia may remove genetic material from the neighboring *MEFV*, causing deregulation of the gene. Less likely, the deletions may remove the mutated region, causing the mutation to disappear, or may remove regulatory elements without affecting the *MEFV* structurally, thereby reducing gene expression. Supporting this hypothesis, in a recent study examining the splicing pattern of *MEFV* and conducting a qualitative analysis of *MEFV* transcripts, lack of some exons due to deletions was determined in symptomatic heterozygous FMF patients (5). Since  $\alpha$  thalassemia is very common and is especially frequent in Mediterranean populations that have a high frequency of FMF, the coexistence of these two genetic diseases is highly likely. Indeed, in the first observation that brought this association to the attention of the medical field,  $\alpha$  thalassemia was determined in every individual with FMF mutation, and this coexistence was inherited to the successive generations (1). Therefore, a special emphasis was made on this heritable coexistence. However,  $\alpha$  thalassemia and FMF should not always be inherited together. In the present observation, for example, the two clinical conditions do not coexist in and have not been coinherited from the same parent. Each parent has only one of the two diseases.

Instead, these two clinical conditions have come together in the index case, and this coexistence led to the clinical symptoms. A meticulous review of the limited data available revealed that deletions determined in the analysis of *MEFV* transcripts in symptomatic FMF carriers may affect almost all exons, more significantly, several and sequential exons are synchronously deleted [such as exons 2,3,4 (del234), or exons 2,3,4,5 (del2345)], deletions are not dependent on the type of FMF mutations, and similar deletions are also present in some controls (individuals who are not carrying the FMF mutation) (5). Those findings basically suggest the potential effect of  $\alpha$  thalassemia deletions on the neighboring *MEFV*. This form of effect is independent of the mutations of FMF; furthermore, FMF mutation is not even required for this effect to occur. In brief, coinheritance of these two genetic disorders is not obligatory. The aforementioned effect of deletion, if any, might be inherited from a parent having both of these two disorders (1), or as seen in the present observation, the two genetic disorders are inherited as one from each parent. Whatever the route of inheritance, either jointly or separately, the point is that when these two clinical conditions join in an individual, clinical symptoms of FMF occur. Actually,  $\alpha$  thalassemia as an acquired abnormality might also be expected to cause clinical symptoms in an asymptomatic FMF carrier. In fact, the example of this acquired type might be the case presented by Sasaki et al (6). In this case, the development of FMF attack in myelodysplastic syndrome (MDS) in a case carrying *MEFV* heterozygous mutation was reported. Although it was emphasized that the first attack of FMF was observed after the initiation of therapy for MDS, and the drug was cited as triggering the clinical symptoms, the MDS itself might have caused this progression; it is known that deletions of the  $\alpha$ -globin gene cluster result in acquired  $\alpha$  thalassemia in MDS (7). Such a deletion in this case might have affected the *MEFV* by any mechanism, and together with the FMF mutation might have given rise to the clinical symptoms.

In the current situation, the following questions are still important and need to be clearly answered: 1-Is concomitant  $\alpha$  thalassemia the only explanatory mechanism for symptomatic FMF patients who carry a single mutation? Most probably not. Deletions resulting in  $\alpha$  thalassemia might be responsible in a subset of the symptomatic FMF carriers. 2-Does each type of deletion resulting in  $\alpha$  thalassemia affect the *MEFV*? Probably not. Some cases of  $\alpha$  thalassemia with FMF are asymptomatic (1). 3-Then which type of  $\alpha$ -globin gene deletions affect the *MEFV*? Probably some large deletions or, more significantly, some critical deletions. Regardless of the type of diseases, the effect of a deletion does not depend on its size alone. While some large deletions are associated with an unexpectedly mild phenotype due to many factors (8), a small deletion affecting a critical region may cause a drastic effect. For FMF, an example of these potential critical regions might be those that have recently been shown to alter *MEFV* gene expression (9). In addition, due to the high frequency of recombination events in  $\alpha$  thalassemia (2), it is difficult to foresee the clinical phenotypes of deletions. 4-Is the direct or indirect effect of deletions on *MEFV* different from that of point mutations? Probably not. When a deletion resulting in  $\alpha$  thalassemia or in another disease in the same genetic localization, such as Rubinstein-Taybi syndrome (RTS) (10), coexists with a single FMF mutation in an individual, characteristic FMF symptoms develop as seen in homozygous disease.

## CONCLUSION

This is a clinical observation presented herein. Since molecular analysis was not available, clarification of the unanswered questions based on this presentation could not be expected. Instead, molecular hematologists/geneticists and their ongoing molecular research would clarify all those questions. However, we do hope that, in the coming years, each new observation of clinicians, who are the first to be aware of the noteworthy cases, will provide a further piece of the puzzle that medical science has long been endeavoring to resolve, and will facilitate its completion.

## Conflict of Interest

No conflict of interest was declared by the authors.

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