Homozygous ß-Thalassemia Associated with Familial Mediterranean Fever in a Turkish Patient

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ABSTRACT

We report here a ß- thalassemia major case (homozygous IVS-1-110 G-A) associated with Familial Mediterranean Fever (FMF) (homozygous 694 Met-Val). Our patient's clinical course revealed a possible synergistic effect between colchicine and desferrioxamine (DFO) However, this could be a only a coincidence, as under colchicine therapy, fever attacks may appear, this may be the topic of a further investigation.

Key Words: Thalassemia, Familial Mediterranean Fever (FMF), Desferrioxamine (DFO), Colchicine.

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INTRODUCTION

ß-Thalassemia belongs to a heterogeneous group of autosomal recessive disorders with a very high frequency in the Mediterranean area; so far, more than 180 different molecular defects have been defined on the ß-globin gene[1]. Familial Mediterranean Fever (FMF) is also an autosomal recessive disorder, characterised by recurrent acute attacks of fever accompanied by abdominal pain, arthritis and pleurisy. The most severe complication of the disease is the development of systemic amyloidosis, ultimately leading to renal failure. The disease is found in especially high frequency in the Sephardic Jews, Armenians, Turks and Arabs[2]. Very recently, the gene likely to cause FMF was cloned, and 3 common mutations in exon 10 (Met 680 Ile, Met 694 Val, Val 726 Ala) were reported. These 3 mutations comprise about 80% of the mutations causing FMF[3-5]. Here we report a ß-thalassemia major case in combination with FMF.

CASE REPORT

A six month old male baby was admitted for the evaluation of pallor and infantile colic. In prenatal history, his mother had FMF and used colchicine after the first trimester of her pregnancy. He was born as intrauterine growth retarded and preterm with gestational age of 28 weeks with a weight of 864 g and a height of 31 cm. On admission, he was pale, had hepatosplenomegaly, his weight was 3050 g, his height was 52 cm and the

head circumstance was 36 cm. Hematological findings and genotypes of his family are summarized in Table 1. Transfusion therapy was started when the Hb level was 7 g/dL after one month. When he reached 8 months, he regularly had fever about twice a week, preceded by chills and accompanied by abdominal pain. Extensive clinical investigations have failed to reveal any definitive microbiological or immunological abnormality. Clinically, his diagnosis was accepted as FMF and he was treated with daily 2 mg colchicine. The frequency and severity of the attacks decreased after a week. Colchicine therapy has been continued. Molecular analysis of FMF, using the previously reported techniques, revealed the genotype to be homozygous for 694 Met-Val[3]. Desferrioxamine (DFO): 40 mg/kg/day was initiated subcutaneously with pump to reduce iron accumulation because a total 28 units red cell were transfused and ferritin level was 5577 ng/mL. The attacks of fever had no and the serum ferritin level dropped to 1080 ng/mL for one year. Now, the patient who is 5 years old, his weight is 12 kg and his height is 93 cm, has no problem except growth and mental retardation. Up to now, a total 37 packed red cell was transfused to him with mean pre and posthemoglobin level is 9.1 and 14.4 g/dL and mean ferritin level is 2414 ng/mL per year. He has been followed up with therapy that daily 40 mg/kg DFO four times per week and daily 2 mg colchicine and there is no the common side effects of colchisine.

DISCUSSION

Administration of effective long-term DFO, maintains long-term survival of the patients, without the complications due to iron overload in thalassemia major[6]. FMF is an autosomal recessive recurrent episodic inflammatory disorder characterized by recurrent short episodes of fever, peritonitis, arthritis, and pleuritis[2,7]. The symptoms and pain of most FMF patients dramatically relieve when beginning colchicine, and the frequency of painful attacks drops abruptly. The common side effects of colchicine are mild and transient[8].

Here we report a patient who has FMF in association with homozygous ß-thalassemia. The patient has been transfused regularly to maintain Hb level between 9-14 g/dL and treated with colchicine (2 mg/day) to prevent the FMF attacks for 4 years. However, attacks didn't disappear completely during the colchicine therapy. After DFO treatment was started, the attacks decreased and stopped. This condition may explain due to synergistic effect of DFO and colchisine or the effect of DFO on FMF or coincidental. In experimental studies, colchicine administration has no effect on biliary ferritin excretion in normal rats, however in iron-loaded rat, it has a fivefold release of biliary ferritin. Colchicine increases the excretion of iron in biliary system and lysosomal enzymes in iron-loaded rat liver[9,10]. Long-term administration of DFO maintains reduction of iron

Table 1. Hematological and molecular data of the family

Data	Patient	Mother	Father
Hb (g/dL)	9.0	10.7	12.7
Htc (%)	27.4	31.8	37.2
RBC (x106/dL)	4.26	4.76	5.64
MCV (fl)	64.4	66.8	66
Hb A1 (%)	1.0	94.2	94
Hb A2 (%)	2.0	5.6	5.8
HbF (%)	97.0	0.2	0.2
FMF mutations	694/694 Met-Val	694/726 Val-Ala	694/N
ß-Thalassemia mutations	IVS 1-110/IVS 1-110	IVS 1-110/N	IVS 1-110/N
Therapy	TRx+DFO+Colchicine	Colchicine	No

concentration in liver, improves liver function and prevents hepatic fibrosis[6]. It is interesting that both colchicine and DFO increases the excretion of iron in experimental studies. Our patient's clinical course revealed a possible synergistic effect between colchicine and DFO. However, this could be a only a colchicine, as under colchicine therapy, fever attacks may appear, this may be the topic of a further investigation.

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