Is There a Thrombotic Tendency in Patients with Familial Mediterranean Fever? A Small Case Series and Review of the Literature

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Abstract

Objectives: Familial Mediterranean fever (FMF) is an auto-inflammatory disease characterized by fever, abdominal pain and pleuritic attacks. It is well known that there is a relationship between inflammation and thrombosis. However, there is very limited knowledge about thrombotic tendency in familial Mediterranean fever (FMF). Here we reported two patients with FMF who developed thrombo-embolic events in the presence of acquired thrombophilic factors. We would also like to review five additionally published FMF cases that have developed thromboembolic events, as well as briefly discuss haemostatic mechanisms in FMF patients.

Methods: We conducted a comprehensive review of the English literature to analyze data on thrombotic or thromboembolic events in patients with FMF. The PubMed, Web of Science, Proquest, and Ovid databases were searched for articles using the term FMF combined with one of the following terms: thrombosis, thromboembolism, deep venous thrombosis, and pulmonary embolism.

Results: In four English articles, we identified five FMF patients, plus our two cases with thrombotic complications. A hereditary or at least one acquired thrombophilic factor was determined in six cases. One patient had not had any thrombophilic factor. M694V mutation was determined in five patients. In six patients, thrombotic events developed under the age of 45 years.

Conclusions: Thromboembolic events may rarely develop in FMF patients with the presence of congenital or inherited thrombophilic disorders.

Key words: Familial Mediterranean fever, inflammation, thrombosis, thromboembolism, thrombophilia

Introduction

It is a well-documented fact that there is a close relationship between inflammation and thrombosis [1]. However, there are very strict case reports showing thrombotic events in patients with FMF in spite of its chronic inflammatory nature [2-4]. With regard to this discrepancy, it was suggested that there is a subtle balance between procoagulant and anticoagulant activities during the attack period. Furthermore, it was suggested that if there is an
additional risk factor for the development of thrombosis apart from inflammation, a thrombotic event may ensue in FMF patients [5, 6]. In this report, we aim to support this notion by presenting two FMF cases that developed thromboembolism. We would also like to briefly discuss haemostatic mechanisms in FMF patients.

**Case 1**
A 21-year-old male patient had been admitted to another hospital with gross oedema. After evaluation of oedema aetiology, the patient was diagnosed as having nephrotic syndrome and AA amyloidosis confirmed by renal biopsy. The patient was diagnosed with FMF because he had had a history of recurrent abdominal pain, fever and erysipel-like erythema since 7 years old. He was put on colchicine at doses of 2 mg a day. The patient was admitted to our hospital with dysarthria, right-side hemiplegia, and right-side central facial paralysis in Feb 2011. Cerebral Computed Tomography showed left cerebral infarct. All congenital and acquired thrombophilic disorders were negative with the exception of positive lupus anticoagulant in a low titre. MEFV mutation was homozygous for M694V mutation. Proteinuria was found to be 3.85 g/24 h. The patient was heparinized and then anticoagulated with warfarin.

**Case 2**
A 30-year-old pregnant woman had presented to the Department of Gynaecology and Obstetrics on August 22, 2010 due to abdominal pain. The patient was at the 34th week of gestation. The patient had also been followed by the Department of Rheumatology pertaining to FMF and polyarthritis. Disease-modifying anti-rheumatic drugs and etanercept (ETN) had been given prior to conception. All the drugs (but colchicine) were discontinued before pregnancy, as the patient did not want to use ETN. Only two days after her admission to the clinic, she was taken to the operation theater due to such symptoms as hemodynamic instability and a lack of fetal heartbeats, which was suggestive of abruptia placenta. To the shock of the obstetrician and general surgeons, the patient had developed widespread cyanosis in the bowels, and unfortunately, neither she nor her baby could be rescued. They attributed the widespread cyanosis in the bowels to mesenteric ischemia with infarcts. Even so, they could not be absolutely sure of their diagnosis, inasmuch as the patient’s family declined the request for autopsy.

**Discussion**
We described two patients with FMF who developed thrombo-embolic events. Even though our first case was free from any congenital thrombophilic disorders, he had an acquired nephrotic syndrome (NS). There is strong evidence suggesting that patients with NS have a high incidence of thrombo-embolic phenomena associated with an abnormally high level of clotting factors [7]. The plasma fibrinogen concentration and fibrinogen turnover increase in relation to the degree of proteinuria and depression of the serum albumin. Moreover, fibrinogen, as an acute-phase reactant, increases in FMF patients both in attack and attack-free periods [8]. Since this protein is an important precursor for fibrin, which is essential for the final clotting pathway, this condition may theoretically contribute to coagulation.

As to our second case, mesenteric infarct probably developed during pregnancy. Work-up for the congenital thrombophilic disorders could not be carried out for this patient, on account of the fact that she had been admitted to hospital as an emergency case. Even so, it is well known that pregnancy is a procoagulant status. Although deep venous thrombosis (DVT) and pulmonary embolism have been reported in pregnancies [9], we lack any histological evidence insinuating mesenteric infarction in our case. Still, what led us to suspect mesenteric infarction was the cyanotic appearance of the bowel system during the surgery. On the other hand, we could not rule out the possibility that our patient may have actually developed mesenteric vasculitis as a part of Henoch-Schonlein purpura or polyarteritis nodosa, because it is not uncommon to observe one of these conditions in the course of FMF [10]. All the same, as was aforementioned, we possess no clinical evidence to ascertain whether our patient had any symptoms of vasculitis, such as fever, purpuric lesions, hypertension, myalgia, etc.

The most striking part of the story of our second case is that she was observed to have periintestinal fluid accumulation on her abdominal pelvic USG, which is the kind of finding that could be mistaken for that seen in peritonitis due to FMF. However, it is possible to observe these findings not only in peritonitis due to FMF but also in mesenteric vasculitis or mesenteric ischemia. With this delicate point in mind, we
suggest that a physician should not immediately attribute abdominal pain and fluid accumulation in an FMF patient with acquired thrombophilic disorder to FMF-related peritonitis, but that he or she should also take into account that these two findings may also be linked to a vascular condition.

In the literature, there are very rare reports showing thrombotic events in FMF patients (Table 1). Sari et al. reported two cases with FMF that developed Budd-Chiari syndrome in the course of FMF [2]. One of the patients had a single mutation in the factor V Leiden, whereas the other was homozygous for MTHFR mutation. The authors suggested that FMF should be regarded as a possible additional thrombotic risk factor in such cases. Aoun et al. reported a child with FMF who developed a stroke [3]. The patient had multiple inherited and acquired risk factors for thrombosis. Ustundag et al. presented a case with FMF that developed SVCS possibly due to obesity and sleep apnea syndrome [4]. Ruiz et al. reported a pulmonary embolism in an FMF patient without having any inherited and acquired risk factor for thrombosis [11]. Reuben et al. reported seven patients with FMF who developed renal failure due to renal vein thrombosis [12]. All their patients had AA-type amyloidosis. However, the authors did not determine whether the patients had additional congenital thrombophilic disorders. Even so, all their patients had NS secondary to amyloidosis. The authors pinpointed the nephrotic syndrome as a major cause of renal vein thrombosis and renal failure.

In the literature, there exist some studies into the coagulation parameters in FMF patients. Aksu et al. showed a hypercoagulable state in attack-free FMF patients [13]. They found shortened TT and prothrombin time and decreased protein C activity and increased levels of human prothrombin fragment F 1+2 in FMF patients without having other predisposing factors for thrombosis. Activated protein C (APC) is a natural anticoagulant that plays an important role in coagulation homeostasis by inactivating the procoagulation factors Va and VIIIa. Reduction of APC may result in hypercoagulability in FMF patients. Demirel et al. studied thrombotic and fibrinolytic markers in FMF patients [5]. They showed prolongation of PT during the attack period. They also showed that PAI-1 levels increased in FMF patients during the attack period compared to the attack-free period. It is well known that PAI-1 is

<table>
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<th>Age/Gender</th>
<th>52/M</th>
<th>9/M</th>
<th>8/F</th>
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<th>21/M Presenting case 1</th>
<th>30/F Presenting case 2</th>
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<tr>
<td>Onset age for FMF</td>
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<td>7</td>
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<td>Childhood</td>
<td>7</td>
<td>3</td>
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<td>Diagnostic age for FMF</td>
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<td>Diagnostic age for thrombosis</td>
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<td>The site of thrombosis</td>
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<td>Stroke</td>
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<td>Mutation for FMF</td>
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<td>M694V (H)</td>
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<td>Obesity Smoking SAS</td>
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<td>LA</td>
<td>-</td>
<td>NS</td>
<td>Pregnancy</td>
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SVCS: Superior vena cava syndrome; BCS: Budd-Chiari syndrome; NS: Nephrotic syndrome; PE: Pulmonary embolism; FMI: Fatal mesenteric embolism; FVL: Factor V Leiden; SAS: Sleep Apnea Syndrome; LA: Lupus anticoagulant; MTHFR: Methylene tetra hydrofolate reductase; H: Homozygous; ND: Not done
produced by endothelial cells and that it inhibits fibrinolysis. PAI-1 is also considered one of the markers of endothelial dysfunction. An increase in PAI-1 levels gives rise to a hypercoagulable condition. On the other hand, Demirel et al. showed increased levels of tissue plasminogen activator (tPA) during the attack period compared to the control group, which is an activator of the fibrinolytic system. The levels of tPA were also high in the attack-free period compared to the control group, but were not of statistical significance. The authors surmised these results as a balance between coagulation and fibrinolysis in vivo. In FMF patients, vW factor and F VIII levels were found not to be different from those of normal controls [5]. Fibronectin (FN) and thrombospondin (TSP) can play a role in coagulation in addition to inflammation. Plasma fibronectin and thrombospondin levels during FMF attack periods were significantly higher after resolution of the acute attacks. There was also a significant correlation between both FN, TSP and CRP levels and WBC counts in two different studies [14].

All the cases shown in Table 1 (except one) had congenital or acquired thrombophilic risk factors for the development of thrombosis. The presence of a procoagulant background that led to the thrombotic complication may be a crucial factor for the development of thrombosis in these FMF patients. When we look at the literature, thrombotic events do not seem to be frequent in FMF patients due to a balance between the coagulant and anticoagulant system. Increased levels of tPA may be a factor for the prevention of further thrombosis. Colchicine usage may be another factor for the preclusion of thrombosis. Colchicine inhibits not only inflammation but also adhesion molecules, such as E and L selectin [15]. Crittenden et al. reported that colchicine use is associated with decreased prevalence of myocardial infarction in gout patients [16]. The authors suggested that the anti-inflammatory feature of colchicine may be a factor for this beneficial effect.

As a result, there seems to be a subtle balance between the coagulation and anticoagulation system in FMF patients. This feature may be a protective factor for the development of thrombosis. In this process, colchicine may also play a role in favor of anticoagulation with anti-inflammatory effects. However, we should keep in mind that thromboembolic events may develop in FMF patients with the presence of congenital or inherited thrombophilic disorders.

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**References**