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Coagulation and Fibrinolysis Abnormalities in Patients with Muscular Dystrophy

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1. Introduction

The cause of the Duchenne muscular dystrophy (DMD) is deficiency of the dystrophin protein leading to dysfunction of many organs. Originally it was thought that the natural history of this disease limits the lifespan of the patients to 20 year. However, positive therapeutic interventions for heart failure, respiratory failure, nutritional management, spinal surgery and the rehabilitation raised the lifespan of patients with DMD in Japan above 30 years of age. (Ishikawa Y, et al. 2011) (Matsumura T, et al. 2011) (Saito T, et al. 2011). Consequently, nowadays complications accompanying the higher survival age of DMD patients should also be considered. This chapter describes a coagulation and fibrinolysis abnormality of muscular dystrophy, and its involvement in the microcirculation disorder accompanying this disease.

2. The old tale of DMD as a microcirculation disorder

Historically before the discovery of dystrophin, a hypothesis was proposed that blood circulation insufficiency due to intravascular obstruction causes muscle necrosis in DMD. This hypothesis was based on muscle histopathology findings similar to necrosis caused by circulation insufficiency. There were some reports that tried to model the pathologic condition of DMD with impaired circulation. However, these trials to reproduce the DMD pathology were unsuccessful. (Bradley WG, et al. 1975) (Gudrun B, et al. 1975) (Leinonen H, et al. 1979)

Meanwhile Miike T, et al. described vascular obstruction and vascular endothelial hyperplasia, namely the blister-like swelling of vascular endothelial cells in the muscle histopathology of non-symptomatic children with DMD, and put forward a hypothesis of the blood flow abnormality that affects the progress of DMD (Miike T, et al. 1987). After the discovery of

dystrophin, the mainstream theory for the pathogenesis of DMD became the muscle destruction due to the membranous fragility related to dystrophin defects. Since then the vascular disorders in DMD have been regarded not important.

3. Thrombosis and embolization as complication of DMD

There are some reports related to thrombosis or embolization of patients with DMD.

In 1982, Matsuishi T, et al. reported a basilar artery occlusion in a case of DMD, in which the pathogenesis of infarction was uncertain. (Matsuishi T, et al. 1982) In 1989, Gaffney JF, et al reported left ventricular thrombus and systemic emboli complicating the cardiomyopathy of DMD. (Gaffney JF, et al. 1989) Authors showed anteroseptal mural thrombus and right atrial thrombus as autopsy findings. Riggs T also reported three terminal DMD cases of cardiomyopathy and pulmonary emboli. (Riggs T. 1990) Author showed thrombus formation of ventricle and pulmonary embolus with a ventilation perfusion scan.

The epidemiologic aspects of DMD-related thromboembolism were addressed by Biller J, et al., who reported the frequency of cerebral infarction in patients with inherited neuromuscular diseases including DMD, Becker muscular dystrophy (BMD), myotonic dystrophy, and Freidrich ataxia. According to their data cerebral infarction was seen in 1. 5% of the cases with these diseases and concluded that cerebral infarction is uncommon in neuromuscular diseases.

4. Pioneer studies of coagulation and fibrinolysis abnormalities of DMD in Japan

Among annual reports of clinical research group for muscular dystrophy in Japan, some reports described cases of cerebral infarction and pulmonary embolism in patients with DMD. Ishihara T, et al. reported series of 15 autopsied cases of DMD/BMD with hemorrhagic pulmonary infarction in 1990. He pointed out that this disorder is an important cause of death in DMD. Matsuka Y, et al. reported a DMD case of cerebral infarction and thrombus formation in the left ventricle in 1991, and described elevated levels of thrombin-antithrombin complex (TAT) and platelet factor 4 (PF4) among many DMD cases with CTR>50% in 1993. Hanajima, et al. reported the occurrence of cerebral infarction of DMD in muscular dystrophy wards in Japan to be 5 / 269 DMD patients aged from 16 to 20 years old. Authors concluded that cerebral infarction is not a rare complication of DMD. (Hanajima, et al. 1996)

Based on these findings the clinical research team for the genetic counseling and the clinical research of the pathology and treatment in muscular dystrophy patients (from 1996 to 1998), that was directed by Ishihara T, proposed a research and intervention project to investigate the blood coagulation disorder complicating the muscular dystrophy. In next section, results of the research in this team are described.

5. Abnormal coagulation and fibrinolysis in DMD

Saito Y, et al. reported hypercoagulable state in patients with DMD. (Saito Y, et al. 1997) By the blood coagulation test of patients with DMD and other neuromuscular diseases at rest condition, the authors showed that abnormal findings appear in many coagulation and fibrinolysis parameters such as thrombotest, TAT, and plasmin- α 2 Plasmin inhibitor complex (PIC) in DMD. Namely, level of thrombotest, which reflects coagulation activity including effect of PIVKA (used for monitoring warfarin treatment), was low compared to normal range in 78% of DMD, TAT level was elevated in 61% of DMD, and PIC level elevated in 40.3% of DMD. Abnormality of the coagulation and fibrinolysis was found in most patients with DMD. The frequency of abnormality was high compared with other neuromuscular diseases.

In this report, the ratio of abnormal value of D-dimer and fibrin and fibrinogen degradation products (FDP) was low in DMD, authors described that coagulation cascade is more enhanced than fibrinolysis cascade in patients with DMD. The coagulation and fibrinolysis abnormality was not associated with age, respiratory function, cardiac activity, and activities of daily living. Authors concluded that muscular dystrophy itself is a risk factor for thrombosis.

Based on examination of relation with the muscle destruction Saito T, et al. reported that coagulation and fibrinolysis abnormality is strongly present in younger patients with DMD, BMD, and Fukuyama congenital muscular dystrophy (FCMD). (Saito T, et al. 2001) They showed significant correlation between serum levels of FDP and MM isozyme of creatine kinase (CK-MM), irrespective of type of dystrophy. Figure 1 shows correlation between FDP and CK-MM of patients with DMD, whereas Figure 2 shows correlation between FDP and D-dimer. Levels of FDP were higher at ambulatory young boy with high CK DMD. Authors speculated that enhanced coagulation and fibrinolysis in DMD, BMD, and FCMD is induced by some components that leak from destructed muscle. It is inferred that the disturbances of the coagulation and fibrinolysis result from the muscle destruction. Increase of both plasma levels of D-dimer and serum levels of FDP is an indirect proof of thrombus having been present in vivo. It means that microcirculation disorder is possibly present in DMD, BMD, and FCMD potentially.

In this study advanced DMD patients with low CK showed no abnormal elevation of FDP and D-dimer. However, even DMD patients in advanced stage, whose CK levels were within normal range, showed coagulation abnormalities, if serum CK increased as a consequence of muscle destruction induced by various causative factors. Saito T, et al. reported activated coagulation cascade in a case of advanced DMD that showed transient elevation of serum CK due to convulsion. (Saito T, et al. 2003) These phenomena are possible sources of pulmonary emboli accompanying DMD. Nakayama T, et al. established that CK elevation preceded the development of pulmonary embolism in patients with DMD (Nakayama T, et al. 2000).

6. Abnormal coagulation and fibrinolysis in cases of dystrophinopathy with heart failure

There is evidence for association between cardiac dysfunction and coagulation disorder. Saito T, et al. reported that levels of TAT and prothrombin fragment (F1+2) in DMD patients

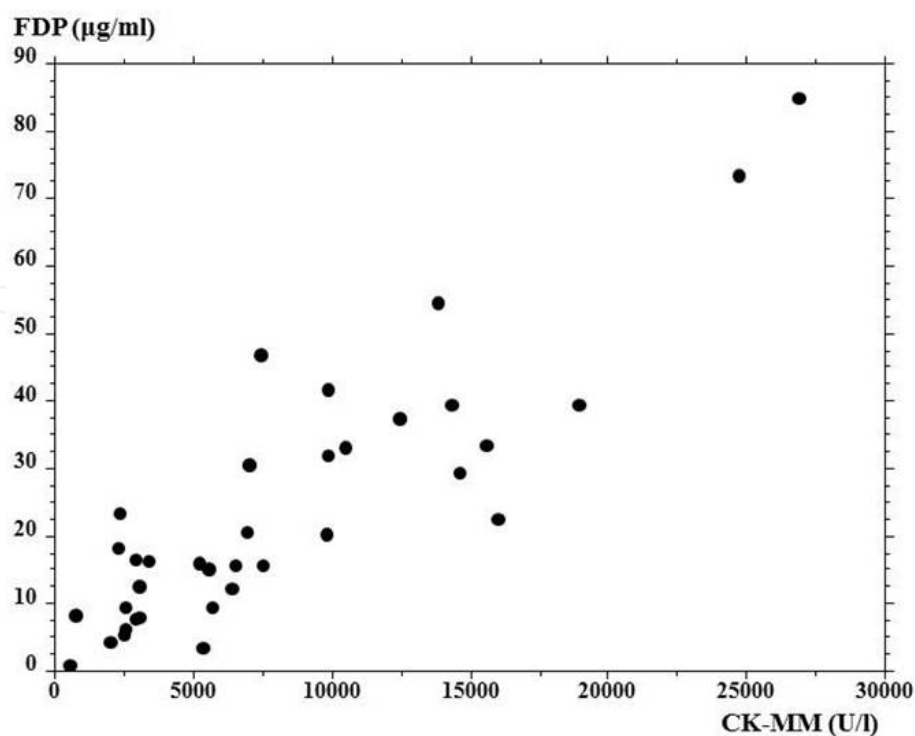


Figure 1. Correlation of serum FDP and CK-MM in patients with DMD, Serum CK-MM level is significantly correlated with FDP. n=36, (modified figure of literature, Saito T, et al. 2001)

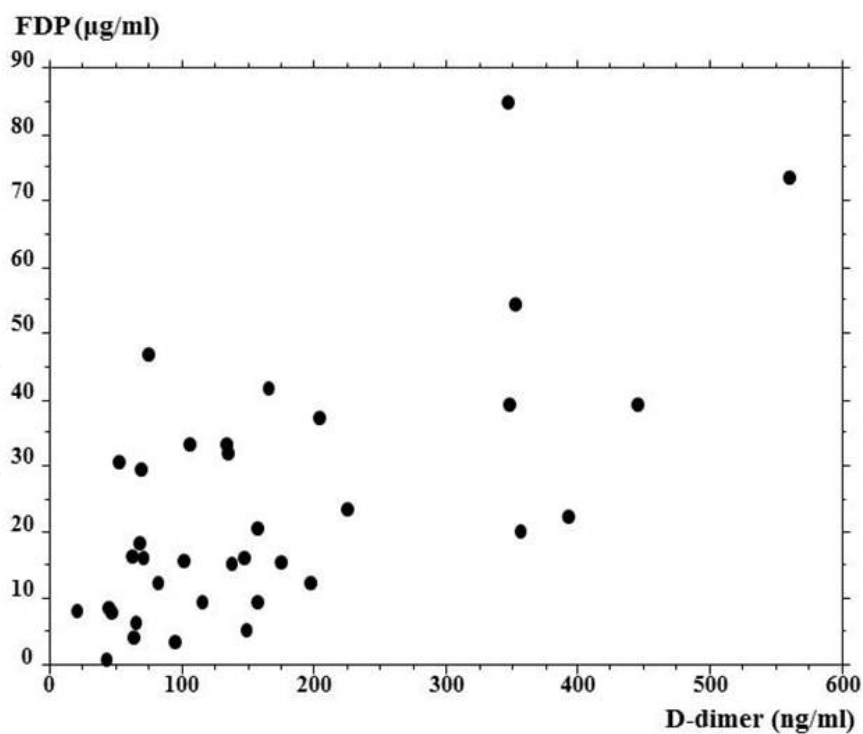


Figure 2. Correlation of serum FDP and plasma D-dimer in patients with DMD, Although correlation between FDP and D-dimer was not significant, both FDP and D-dimer elevated in DMD patients. n=36 (modified figure of literature, Saito T, et al. 2001)

with the markedly depressed cardiac function were significantly elevated compared to DMD patients with preserved cardiac function. Authors concluded that activated coagulation is associated with cardiac dysfunction in patients with DMD. (Saito T, et al. 2005) Porreca E, et al. also reported similar findings in patients with dystrophinopathy including BMD. (Porreca E, et al. 1999) These abnormalities probably induce cerebral infarction through a mechanism similar to the one observed in idiopathic cardiomyopathy. Ikeniwa C, et al. reported two cases of DMD with dilated cardiomyopathy and cerebral infarction. (Ikeniwa C, et al. 2006)

7. Studies of other factors affecting coagulation and fibrinolysis status

In addition to the cases described above, the clinical research group for muscular dystrophy in Japan reported that infectious diseases activate coagulation cascade by increasing the level of fibrinogen resulting in elevation of D-dimer. However, this acute-phase reaction induced by infection is observed generally in normal subjects too.

An interventional study was also proposed in the form of a clinical trial to administer warfarin for DMD/BMD patients with high risk of thrombosis. Within its framework information regarding the coagulation status of 190 DMD/BMD patients in muscular dystrophy wards in Japan was collected abnormal rate of TAT was 36. 0%, and that of F1+2 was 51. 2% in DMD patients, which demonstrated that enhanced blood coagulation was dominant in DMD patients. However, the number of patients recruited in this clinical trial was too small, so the trial was not started. Instead of clinical trial, they proposed substitute treatment, namely improving congestion in venous return of bedridden patients with DMD, and prevention of dehydration.

8. Platelet abnormalities in DMD

Forst J, et al. reported a significant deficiency of platelet adhesion and ristocetin induced aggregation as well as a marked reduction of expression of glycoprotein IV, although normal plasmatic coagulation and a slight but not significant increase of bleeding time was observed in DMD patients (Forst J, et al. 1998). Authors speculated that the platelet function deficiency occurs because of a decompensation of platelet adhesion as well as aggregation capacity in major spinal surgery, although the deficiency of platelet function in DMD patients does not affect ordinary life or minor surgery.

Further, Matsumura T, et al. reported a case of DMD complicated by thrombotic thrombocytopenic purpura (TTP). In their report, TTP was confirmed by decreased activity of von Willebrand factor cleaving protease and activity plasma exchange was successful for the patient (Matsumura T, et al. 2003).

9. Pathogenetic aspects of the coagulation abnormalities in Duchenne muscular dystrophy

From the point of view that coagulation disorders induce microcirculation abnormalities, Saito T, et al. speculated that hypoxic and ischemic condition might exist in DMD. They reported that elevated levels of VEGF are observed in dystrophinopathy patients, and supposed that these are induced by relative hypoxic and ischemic condition. (Saito T, et al. 2009) However, these conditions were marked in advanced DMD patients rather than young boy with DMD.

On the other hand, it has been considered that circulation abnormality may participate in disease progression of DMD, which has not been evaluated for a long time since dominance of membrane theory. (Lombard JH. 2011) Functional muscle ischemia has been reported in patients with DMD. (Sander M, et al. 2000) Defect of nNOS due to dystrophin absence induce functional muscle ischemia related muscle exercise, which can induce microcirculation insufficiency of muscle tissue. Asai A, et al. reported effectiveness of Phosphodiesterase-5 Inhibitor to mouse model of muscular dystrophy by improving microcirculation of muscle tissue. (Asai A, et al. 2007)

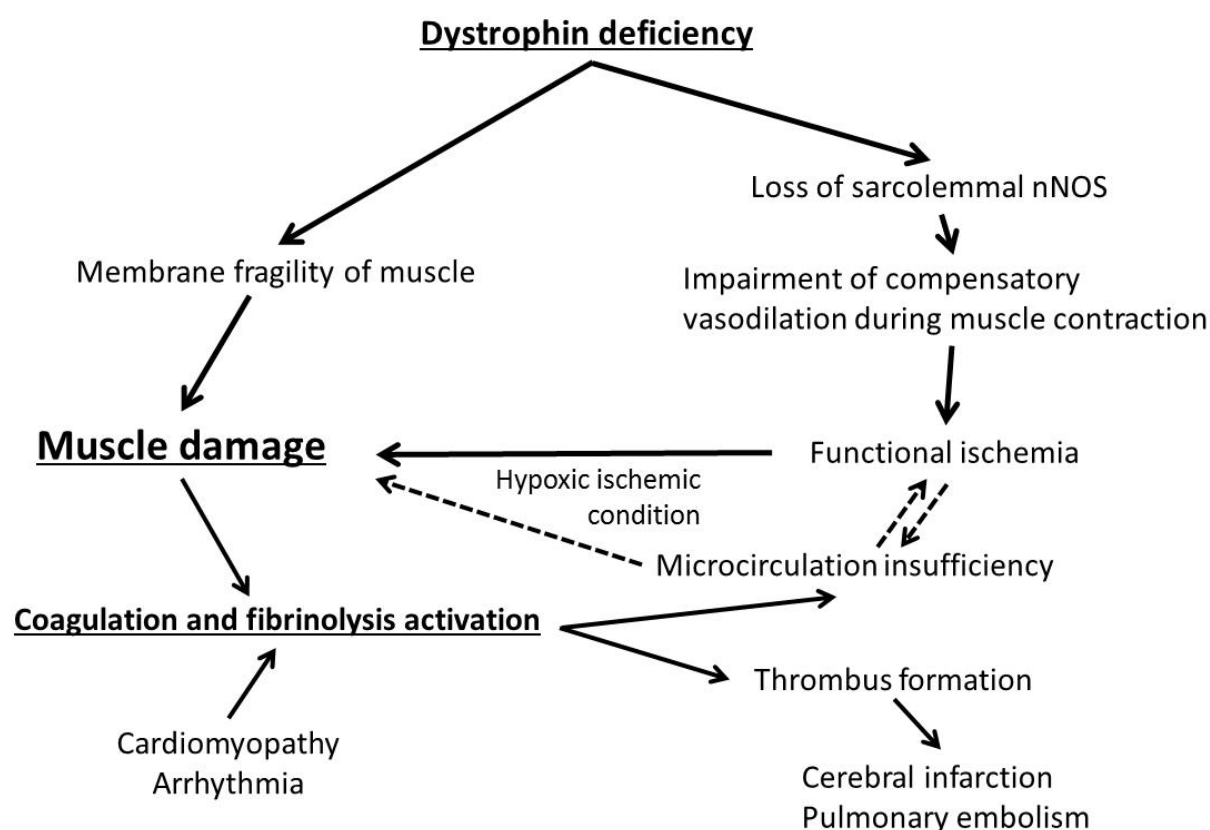


Figure 3. Muscle destruction process and the relation to coagulation and fibrinolysis abnormalities in DMD patients

In Figure 3, I summarize the muscle destruction process and the relation to coagulation and fibrinolysis abnormalities in DMD patients. The origin of DMD is dystrophin deficiency. Dystrophin deficiency induces functional muscle ischemia as well as membrane fragility of muscle, leading to muscle destruction. Muscle destruction activates coagulation and fibrinolysis cascade (, which may be similar to rhabdomyolysis). Activated cascade induces microcirculation insufficiency affecting functional muscle ischemia derive from dystrophin deficiency. On the other hand, cardiomyopathy and arrhythmia cause thrombus formation with mechanism similar to idiopathic dilated cardiomyopathy, which can cause cerebral infarction and pulmonary embolism. Moreover, transient muscle damage even in advanced DMD patients activates coagulation cascade leading to cerebral infarction and pulmonary embolism.

Therefore, improving microcirculation insufficiency, and coagulation and fibrinolysis abnormalities may lead to improving disease progression and prevention of complications in DMD patients. Now, the level of peripheral circulating CD34 positive cells, namely endothelial circulating progenitor cell related with vascular homeostasis, functional maintenance and angiogenesis, is evaluated whether it can be the biomarker reflecting microcirculation abnormality and disease progression of DMD (Saito T, et al. 2013).

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