The Prevalence of Thrombophilia in Idiopathic Osteonecrosis of The Hip

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Background: *Thrombophilia is the propensity to develop thrombosis (blood clots) within the vein or artery due to an abnormality in the system of coagulation. It is one of the pathophysiological causes of osteonecrosis of femoral head (ONFH). Previous studies showed that the prevalence of thrombophilia was 1-15% in normal population. There are two types of osteonecrosis of the femoral head, primary osteonecrosis (idiopathic osteonecrosis) and secondary osteonecrosis from other known conditions. There is no previous report of the prevalence of thrombophilia in idiopathic osteonecrosis of the femoral head in Thailand.*
Objective: *To study the prevalence of thrombophilia in Thai patients with idiopathic osteonecrosis of the femoral head.*
Material and Method: *Fifty-five patients with osteonecrosis of femoral head were enrolled in this study. Forty patients had idiopathic osteonecrosis and 15 patients had secondary osteonecrosis. The blood examination of Factor V Leiden mutant, Factor VIII, Protein C, Protein S and Antithrombin III were completed in all subjects.*
Results: *All patients with idiopathic ONFH had bilateral hip involvement. The prevalence of thrombophilia in idiopathic ONFH was 32.5% (13/40). The protein C, protein S deficiencies, and increased factor VIII were the common types of abnormal coagulation in idiopathic ONFH.*
Conclusion: *Patients with idiopathic osteonecrosis of the femoral head had a high prevalence of thrombophilia at about 32.5% in contrast to 1-15% in the normal population. The present study suggested that thrombophilia maybe a risk factor of idiopathic osteonecrosis of the femoral head.*

Keywords: *Thrombophilia, Osteonecrosis of femoral head, Idiopathic osteonecrosis*

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The osteonecrosis of the hip is the condition of decreasing bone marrow and trabecular bone that is the cause of deficiency in blood supply. The osteonecrosis of the hip can be divided by principle causes into post-traumatic osteonecrosis of the femoral head and non-traumatic osteonecrosis of the femoral head. In 1934, Phemister[1] showed in his study that abnormal vessels from thrombolism and embolism could affect the deficiency of blood supply in the non-traumatic osteonecrosis group, called "avascular necrosis or ischemic necrosis". In 1961, Nison[2] reported that a 28-year old male patient with history of thrombosis was diagnosed with skeletal abnormality and then osteonecrosis later. Therefore, there have been more studies about the correlation between abnormal hemostasis and non-traumatic osteonecrosis of femoral heads. Boettcher[3] reported that the change of hemostasis related to the etiology of non-traumatic osteonecrosis of the femoral head like the study of Egan R et al[4] or Nagasawa K et al[5]. In 1974, Jones et al showed that intravascular coagulation and fibrin thrombosis propagation were the etiology of osteonecrosis. In 1994, Glueck[6] concluded that coagulation disorder affected the development for osteonecrosis of the femoral head.

Thrombophilia, or hypercoagulability, is the propensity to develop thrombosis (blood clots) within veins or arteries. The etiology of thrombophilia comes from abnormal hereditary or acquired (secondary

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thrombophilia) causes. Egeberg[7] reported the insufficiency of antithrombin III and thromboembolic complication in one family and then the insufficiency of protein C and protein S were reported[8]. Rabdin and Sackett[9] concluded that the lack of antithrombin III, protein C, protein S were the causes of hypercoagulable state. From the previous studies[1,10-13] about prevalence of thrombophilia, resistance to the activated protein C (APC resistance) were the most common finding in thrombophilia. Normally antithrombin, protein C and protein S deficiency are found less than 1% in normal population but 5-10% in venous thrombosis. A few studies[14,15] in Thailand found deep vein thrombosis (DVT) of 61% after total knee arthroplasty and one study showed five critical risk factors to develop DVT. One study[16] revealed 47.9% positive venography of postoperative hip fracture.

Over the last 20 years, there have been many studies in thrombotic and fibrinolytic pathways. Therefore, the topic of thrombophilia has been developed simultaneously. Thrombophilia effects vessel obstruction and hypofibrinolysis with inability to dissolve blood clots. Thrombophilia has been studied whether it correlates to osteonecrosis of the femoral head, or of the jaws and osteonecrosis of the femoral head in children or Perthes disease[17-24].

In the recent year, knowledge of osteonecrosis of the femoral head has increased suggesting that there are multifactorial factors to develop osteonecrosis *e.g.* excessive corticosteroid use[25-31], alcoholism[32-34], hemoglobinopathy[35-37], pregnancy[38-40], hyperboric exposure[41], autoimmune disease[42,43], and hip traumatic injury[44-46].

Material and Method

This study was conducted between June 2004 and June 2006 in Phramongkutklao, a 1000-bed tertiary care academic hospital. All patients were admitted with diagnosis of osteonecrosis of the femoral head were recruited. Osteonecrosis was documented by anteroposterior and frog-leg lateral radiographs of both hips and by MRI evaluation. MRI was used to confirm the diagnosis of osteonecrosis. A consensus diagnosis was made by a three-orthopedist committee, blinded to patients' clinical status, age, and hip symptoms. Those patients with pregnancy, estrogen use, drugs induced coagulopathy, history of blood disease, and history of malignancy were excluded.

Fifty-five patients were included in this study (22 females and 32 males). The average age was 43.45 $\pm$ 12.17 years (23-79 year). All patients were examined by a complete blood count with platelet count, Factor V Leiden mutation, Factor VIII , anti-thrombin III, Protein C, Protein S. Thrombophilia included by positive Factor V Leiden mutation, Factor VIII > 200% , antithrombin III < 75 % , Protein C < 70%, and protein S < 60%. Plain film x-rays of both hips and an MRI were completed later. Diagnosis of osteonecrosis of the femoral head was diagnosed by three orthopedists and two radiologists from Phramongkutklao hospital.

Results

In the present study, the prevalence of thrombophilia in osteonecrosis of the femoral head in Thai patients was revealed. The blood examination laboratory of thrombophilia, clinical signs and symptoms and plain films are important documents to diagnose osteonecrosis of the femoral head and to manage the treatment. Fifty-five patients had osteonecrosis of the femoral head. Fifty patients (90.9%) had Bilateral osteonecrosis of the femoral head and five patients (9.1%) had unilateral osteonecrosis of femoral head. The diagnoses were idiopathic ONFH 40/55 (72.7%), steroid-induced ONFH 10/55 (18.2%), and post traumatic ONFH 5/55 (9.1%). All the idiopathic ONFH had bilateral hip involvement.

In the bilateral ONFH group, the average time of symptoms in another hip joint after the first hip joint symptom was 11.8 months (6-24 month). The average time in idiopathic ONFH, steroid induced ONFH, and post-traumatic ONFH were 10.8, 13.8 and 15 months respectively. In the 105 hip joints, 40% were on Figat & Arlet stage II and 26.7% were on Figat & Arlet stage III.

Idiopathic ONFH patients showed at least 1 abnormal blood examination (Factor V Leiden mutant, Factor VIII, Protein C, Protein S, Anti thrombin III) in 13 of 40 patients (32.5%), and one patient had both protein C and protein S deficiency.

No thrombophilia was found in 10 steroid-induced ONFH and abnormal Antithrombin III deficiency was found in two posttraumatic ONFH.

Discussion

Thrombophilia is one of the etiologies for ONFH[1,3,4,22] and leads to increase intraosseous venous pressure and to impair arterial flow, osseous hypoxia, and bone death. The knowledge of thrombotic fibrinolytic pathway and an advanced laboratory are pre-requisites to study of the etiology of idiopathic ONFH, which is the most common type of ONFH. Jones[47] showed that intravascular coagulation and

Table 1. Number of ONFH patients

Etiology of the diseases	Number of ONFH (n = 55)		
	Unilateral	Bilateral	Total
Idiopathic ONFH	-	40 (72.7%)	40 (72.7%)
Steroid induced ONFH	1 (1.8%)	9 (16.4%)	10 (18.2%)
Post traumatic ONFH	4 (7.2%)	1 (1.8%)	5 (9.1%)
Total	5 (9.1%)	50 (90.9%)	55 (100%)

Table 2. Figat & Arlet staging in 105 hips of ONFH patients

ONFH (n = 105 hips)	Ficat & Arlet staging			
	I	II	III	IV
Idiopathic ONFH (80 hips)	20	33	23	4
Steroid induced ONFH (19 hips)	1	8	5	5
Post traumatic ONFH (6 hips)	-	1	-	5
Total (105 hips)	21 (20%)	42 (40%)	28 (26.7%)	14 (13.3%)

Table 3. Results of blood examination in 40 idiopathic ONFH patients

Blood examination results						
Normal	Positive factor V leiden mutant	Increased factor VIII	Protein C deficiency	Protein S deficiency	Antithrombin III deficiency	Protein C & protein S deficiency
27 (67.5%)	1 (2.5%)	3 (7.5%)	3 (7.5%)	3 (7.5%)	2 (5%)	1 (2.5%)

fibrin-platelet thrombosis was the beginning of the obstruction of blood vessels to the femoral head leading to the development of bone necrosis. Glueck et al[6] reported that thrombosis could obstruct venous outflow, increase intramedullary hypertension, decreased arterial perfusion and then develop hypoxia-anoxia and bone infarction. The prevalence of thrombophilia in the normal population is 1-15%[3-6,47,52,53]. In the present study, patients with idiopathic osteonecrosis of the femoral head had a high prevalence of thrombophilia at about 32.5% (at least one abnormal blood examination result). Limited by the small numbers of patients with idiopathic osteonecrosis of the femoral head, the present study could not suggest that thrombophilia was associated with idiopathic osteonecrosis of the femoral head but concluded a high prevalence of thrombophilia in idiopathic osteonecrosis of the femoral head.

Thrombophilia can be hereditary or acquired. In the present study, PCR-DNA analysis revealed that the most common abnormal coagulation was abnormal hereditary[54] including Protein C and Protein S autosomal dominant abnormal mutation. Thrombophilia increased the tendency of thrombosis in vessels and led to osteonecrosis of the femoral head. As a result, the high percentage of prevalence for thrombophilia in idiopathic ONFH maybe one of the risk factors for idiopathic osteonecrosis of the femoral head. Further study with a larger sample size is suggested.

Conclusion

The prevalence of thrombophilia in idiopathic osteonecrosis of the femoral head was 32.5%. This prevalence was higher than previous studies in the normal population. This study suggested that

thrombophilia maybe one of risk factors of idiopathic osteonecrosis of the femoral head.

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ความชุกของภาวะการณ์แข็งตัวของเลือดในโรคข้อกระดูกสะโพกตายชนิดไม่ทราบสาเหตุ

ธไนนิธย์ โชตนภูติ, ดนัย หีบท่าไม้, มนตรี ชูวงศ์, กฤษณ์ กาญจนฤกษ์

***ภูมิหลัง**: ปัจจุบันมีการศึกษาเพิ่มมากขึ้นเพื่อที่จะอธิบายถึงสาเหตุของการเกิดโรคข้อกระดูกสะโพกตาย (Osteonecrosis of femoral head) ซึ่งมีภาวะลิ่มเลือดอุดตันของทั้งหลอดเลือดดำและแดง โดยภาวะดังกล่าว อาจส่งผลให้เกิดการอุดตันของหลอดเลือดที่เลี้ยงข้อสะโพกทำให้เกิดการตายของข้อกระดูกสะโพกตามมา สาเหตุของภาวะการณ์แข็งตัวของเลือด อาจเกิดจากภาวะผิดปกติทางพันธุกรรม (Hereditary) หรือเกิดขึ้นภายหลัง (Secondary thrombophilia) ซึ่งตามรายงานพบความผิดปกติ พบได้ประมาณ 1-15% ในประชากรทั่วไป ในการศึกษาครั้งนี้มีวัตถุประสงค์เพื่อศึกษาถึงความชุกของภาวะการณ์แข็งตัวของเลือดในคนไทยที่สัมพันธ์กับกลุ่มผู้ป่วยข้อกระดูกสะโพกตายชนิดไม่ทราบสาเหตุ (Idiopathic osteonecrosis of femoral head) ซึ่งยังไม่มีการศึกษาในประเทศไทยอย่างชัดเจน*

***วัตถุประสงค์**: เพื่อศึกษาความชุกของภาวะการณ์แข็งตัวของเลือด ในผู้ป่วยโรคข้อกระดูกสะโพกตายชนิดไม่ทราบสาเหตุในโรงพยาบาลพระมงกุฎเกล้า*

***วัสดุและวิธีการ**: เก็บเลือดผู้ป่วยที่วินิจฉัยภาวะข้อกระดูกสะโพกตาย จำนวน 55 คน เป็นกลุ่มที่ไม่ทราบสาเหตุจำนวน 40 คน กลุ่มที่ทราบสาเหตุ จำนวน 15 คน ส่งตรวจผลเลือด 5 ชนิด คือ Factor V Leiden mutant, Factor VIII, protein C, protein S และ Antithrombin III*

***ผลการศึกษา**: ในผู้ป่วยโรคข้อกระดูกสะโพกตายชนิดไม่ทราบสาเหตุ จำนวน 40 คน (100%) มีพยาธิสภาพที่สะโพกทั้ง 2 ข้างทั้งหมด และพบว่าในจำนวนนี้มี 13 ราย (32.5%) ที่มีภาวะการณ์แข็งตัวของเลือดชนิดที่มีสาเหตุจาก protein C & protein S deficiency มากที่สุด*

***สรุป**: ในการศึกษานี้พบว่า ในผู้ป่วยโรคข้อกระดูกสะโพกตายชนิดไม่ทราบสาเหตุ มีความชุกของภาวะการณ์แข็งตัวของเลือดค่อนข้างสูง (ร้อยละ 32.5) เมื่อเทียบกับคนทั่วไป (ร้อยละ 1-15) ซึ่งอาจอธิบายถึงเรื่องความเสี่ยงของโรคข้อกระดูกสะโพกตายในกลุ่มที่ไม่ทราบสาเหตุได้ และอาจเป็นแนวทางการพัฒนาและรักษาตลอดจนป้องกันภาวะนี้ได้ โดยเข้าไปแก้ไขกลไกการเกิดภาวะนี้โดยตรงด้วยการใช้ยาในผู้ป่วยที่มีความเสี่ยงในกลุ่มนี้*