

Deep Vein Thrombosis is Not Rare in Asia—The Singapore General Hospital Experience

L H Lee,**FAMS, MBBS, M Med*, K Q Gu,***PhD*, D Heng,****FAMS, MRCP, M Phil*

Abstract

Introduction: Venous thromboembolism (VTE) is perceived to be rare in Asia, but our recent clinical experience at Singapore General Hospital (SGH) suggests otherwise. Between 1996 and 1997, there were 388 cases of confirmed deep vein thrombosis (DVT). **Materials and Methods:** All patients with symptomatic DVT confirmed by duplex ultrasound studies from January 1996 to December 1997 were retrospectively studied. Their case notes were searched for a record of predisposing risk factors. **Results:** Ultrasound imaging indicated acute thrombosis in 320 patients (82.5%), and previous, but not acute thrombosis in 68 patients (17.5%). The overall frequency rate of acute DVTs was 15.8 per 10,000 hospital admissions. The average age of patients with acute thrombosis was 58.2 years. 9.2% of patients developed pulmonary embolism (PE). Their most frequently recorded clinical predispositions were immobilisation (67%), malignancy (33%) and recent surgery (30%). One hundred and thirty patients were tested for antithrombin, protein C or protein S deficiency, and the presence of antiphospholipid antibody and 45 (35%) were found to have at least 1 positive result. **Conclusion:** DVT is not uncommon in Singapore. Our frequency rate of acute DVT of 15.8 per 10,000 admissions is much higher than previously reported rates of 2.8 and 7.9 per 10,000 admissions in 1990 and 1992, respectively. These findings confirm the need for increased awareness of VTE in Asian populations, and support the relevance of systematic studies of thrombosis risk and prophylaxis in Asia.

Ann Acad Med Singapore 2002; 31:761-4

Key words: Pulmonary embolism, Risk factors for DVT, Thrombophilia, Venous thromboembolism

Introduction

Deep vein thrombosis (DVT), pulmonary embolism (PE), the postphlebotic syndrome and recurrent venous thromboembolism (VTE) are important and often preventable causes of early morbidity or death and of long-term disability in western populations. The reported annual incidence of VTE is about 2 per 10,000 persons in Scotland.¹ In England, the community-based Worcester Study found that DVT develops in 4.8 per 10,000 people each year, and in 0.9% of hospitalised patients.² As a result, there is a high level of diagnostic awareness and the widespread application of consensus group guidelines on thrombosis risk, thrombosis prevention and thrombosis management.³

By contrast, it is widely thought that DVT and PE are rare in Asia^{4,5} and that VTE is mostly a 'Caucasian' problem. This view is bolstered by the rarity of some prothrombotic clotting factor polymorphisms (factor V Leiden and prothrombin G20210A) in Asia.^{6,7} As a result, the study of VTE in Asian populations has attracted limited attention.

Our clinical observations at Singapore General Hospital (SGH) suggest that while DVT may not be as common in

Singaporeans as in Caucasian people, it is certainly not rare in Singapore. Three hundred and eighty-eight patients had symptoms of DVT confirmed by duplex ultrasound imaging at SGH during the 2-year study period (1996-1997). This retrospective study was done to describe the clinical characteristics of these patients and identify their risk factors for thrombosis.

Materials and Methods

From January 1996 and December 1997, there were 202,869 hospital admissions to SGH. A total of 388 consecutive symptomatic patients with DVT confirmed by duplex ultrasound studies were identified from records held by our vascular laboratories of the departments of cardiothoracic surgery and general surgery. This would have captured almost all the patients with DVT as the duplex ultrasound is the investigation of choice in this hospital for the confirmation of DVT in symptomatic patients. Nonetheless, the occasional few patients who had DVT confirmed by other investigations, such as the venogram, will be missed. All patients had symptoms of acute DVT or symptoms of postphlebotic venous

* Consultant Haematologist

Department of Haematology, Singapore General Hospital

** Epidemiologist

*** Clinical Epidemiologist

Clinical Trials & Epidemiology Research Unit, National Medical Research Council

Address for Reprints: Dr Lee Lai Heng, Department of Haematology, Singapore General Hospital, Outram Road, Singapore 169608.

insufficiency. Their inpatient medical notes were searched retrospectively for information about their clinical presentation and predisposing risk factors, including the results of laboratory testing for thrombophilia. The clinical information was then recorded in a structured record form with an agreed checklist of known thrombotic risk factors and other information. Demographics of patients with DVT were compared with those of the entire inpatient population for the period. Results were tabulated and analysed using the SPSS (Version 8) program.

Results

The presence of DVT was confirmed in 388 symptomatic patients with duplex ultrasound imaging. Three hundred and twenty patients were considered to have recent DVT and in 68 the findings were more consistent with previous DVT. The patients with previous DVT had their first acute event between 1989 and 1995.

Between January 1996 and December 1997, there were 202,869 admissions of 54,142 patients to the adult wards of SGH. All patients, 12 years and above, were admitted to the adult wards in SGH during the study period. The frequency rate of all confirmed acute DVT was 15.8 per 10,000 admissions.

Patient Characteristics

A comparison of the demographic characteristics of patients with DVT and the adult hospital population is shown in Table I. The age of the DVT patients ranged from 18 to 92 years, with a mean age of 58.2 (standard deviation \pm 16.5) years. The age of the hospital population ranged from 12 to 128 years, with a mean age of 44.3 (standard deviation \pm 16.7) years. The patients with DVT were older than the general hospital population ($P < 0.0000$, t -test) and were also slightly less likely to be Chinese or Malay ($P = 0.013$, chi-square test). Their age distribution was similar across ethnic groups ($P = 0.11$). The most frequent concomitant medical illnesses were hypertension (37.6%), diabetes mellitus (23.5%), hyperlipidaemia (14.2%) and

congestive heart failure (6.2%).

Extent of DVT

DVT was proximal in 331 patients (85%) and extended to the inferior vena cava at presentation in 22. In another 26 patients (6.7%), the DVT was limited to the calf veins. Thirty-two patients (8.2%) had upper limb DVT, and this was associated with proximal lower limb DVT in 1 patient. Thirty-seven patients (9.5%) had symptoms of PE confirmed by a high probability V/Q lung scan or a positive spiral computed tomography angiogram of the chest.

Clinical Predispositions to DVT

Most patients (83.5%) had a record of at least 1 predisposing risk factor for thrombosis; 34.8% had 1, 35.3% had 2 and 13.4% had 3 or more risk factors at the time of presentation. The patient-related risk factors are listed in Table II. The most frequently recorded risk factors were immobility in 260 patients (67%), concomitant malignancy in 129 (33%) and recent surgery in 106 (30%). Recent surgery was arbitrary defined as a major operation within the previous 30 days.

Immobility was arbitrary defined as bed rest for at least 3 days preceding the onset of symptoms. Immobility was attributed to recent surgery in 39% of cases, advanced cancer in 25%, a stroke or other neurological condition in 21%, pneumonia or another infection in 17%, and to various acute or chronic medical conditions in 18%.

There were 126 patients with a concomitant malignancy and 3 patients with double malignancies. Further analysis of the types of malignancy is shown in Table III. Forty-one (32%) patients with underlying malignancies had recent surgery and 57 (44%) had secondary tumours when they first presented with DVT.

Eight patients developed DVT during pregnancy and 4 developed DVT after a caesarean section.

Predisposing medical disorders included a nephrotic syndrome in 7 patients and polycythaemia rubra vera in 2. Patients with a recurrence of VTE developed their first thromboembolic episode 2 to 12 years earlier.

TABLE I: RACE AND AGE PROPORTIONS

	Study population (%)	Hospital population (%)
Race		
Chinese	72.9	77.0
Indian	10.1	7.6
Malay	11.6	14.1
Others	5.4	1.4
Age (y)		
<20	0.7	4.5
20-39	15.5	39.8
40-59	29.4	35.3
60-79	47.2	18.7
80 & above	7.2	1.6

TABLE II: PATIENT-RELATED RISK FACTORS

	No. (%)
Immobilisation	260 (67)
Underlying malignancy	129 (33.2)
Surgery	115 (29.6)
Previous DVT	35 (9)
Pregnancy	12 (3.1)
Medical Disorders	9 (2.3)
Family history of VTE	4 (1)
Family history of thrombophilia	2 (0.5)

DVT: deep vein thrombosis; VTE: venous thromboembolism

TABLE III: MALIGNANCIES

Types of malignancies (no.)	No.	(%)
Gastrointestinal – appendix (1), colorectal (28), stomach (8), pancreas (2), oesophagus (1)	40	(31.0)
Gynaecology – cervix (12), endometrium (8), ovary (8)	28	(21.7)
Respiratory – larynx (2), lungs (11)	13	(10)
Breast	11	(8.5)
Haematology – lymphoma (9), leukaemia (1), myeloma (1)	11	(8.5)
Neurology – brain (6)	6	(4.7)
Urinary tract – renal (3), ureter (1), bladder (2)	6	(4.7)
Others	14	(10.9)

These patient-related risk factors were further analysed according to 3 age groups — less than 40 years, 41 to 60 years and above 60 years. Surgery was present in 18.6%, 30.4% and 33%, while cancer was present in 12.9%, 27% and 89% in each group, respectively. It is evident that cancer and causes of immobilisation are problems associated with advancing age.

Upper Limb DVT

There were 32 patients with arm vein thrombosis, of which 17 had malignancies involving the lungs, mediastinum and thorax. Only 1 patient had a central venous line *in situ* and she had concomitant acute lymphoblastic leukaemia. Five patients had surgical procedures involving vascular structures of the upper limbs or thorax (4 had creations of arterial venous fistula for haemodialysis and 1 had coronary arterial bypass using the internal mammary vein). One out of these 5 patients had concomitant brain glioma and the other 4 did not have any tumour. One patient who did not have any apparent thrombotic risk factor was eventually found to have protein C deficiency.

Postoperative DVT

One hundred and fifteen patients had developed DVT after surgery and none had received any form of

thromboprophylaxis. Their age, sex and ethnic distributions were similar to those of DVT patients without predisposing surgery. Sixty-four per cent developed symptoms within 14 days, 80% within 21 days, and 20% between 21 and 30 days after surgery. Fifty-four per cent of operations were on the abdomen or pelvis, 23% on the hip or lower limbs, and the rest on the head (9%), thorax or upper limbs (8%), or spine (6%). Forty-one (36%) patients with recent surgery also had a concomitant cancer. Excluding surgery, there was 1 other predisposing risk factor in 65 patients (57%) and 2 risk factors in 44 (38%). Only 6 operated patients had no risk factors for DVT other than their surgery. Comparison with non-operated patients suggested that surgical patients had more non-surgical risk factors for DVT (an average of 1.33 compared with 1.015; $P < 0.001$).

Thirty-five surgical patients (30.4%) had further tests for thrombophilia and 7 (20%) were found to have at least 1 abnormality.

Results of Thrombophilia Testing

A group of patients were investigated further for the following prothrombotic risk factors: antithrombin deficiency, protein C deficiency, protein S deficiency and anticardiolipin antibody (Table IV). There was no preset criterion for thrombophilia studies. Whether the patients were tested or not were depended on the physician's discretion and unit practice. Hence, we found that the patients were subjected to varying numbers of thrombophilic tests. One hundred and ninety-two patients had tests for one or more of these tests and 63 (32.8%) yielded a positive result. One hundred and thirty patients had all 4 tests done and 45 (35%) had 1 or more abnormalities.

Incidentally, 2 patients from this study were found to have Factor V Leiden positive as a result of another study⁸ by the same department; both were of non-Chinese descent — 1 Indian and 1 Malay.

Discussion

Contrary to general perceptions, VTE is commonly seen in Asians. Indeed, results of recent post-mortem studies have also shown that VTE is far more common than perceived.^{9,10} VTE is also one of the leading causes of maternal mortality in Singapore.¹¹ We found that the incidence of DVT was substantially higher than previously

TABLE IV: THROMBOPHILIA RISK FACTORS

Thrombophilia tests	No. tested	No. positive (%)	No. of abnormal tests for the 130 patients who had all 4 thrombophilia tests (%)	No. of abnormal results for patients who had less than 4 tests done (%)
Antithrombin deficiency	152	15 (9.9)	13 (10.0)	2 (9)
Protein C deficiency	149	18 (12.1)	14 (10.8)	4 (21)
Protein S deficiency	147	18 (12.2)	15 (11.5)	3 (18)
Anticardiolipin antibody	171	18 (4.6)	7 (5.4)	11 (27)

reported. Earlier studies from Hong Kong,¹² Malaysia¹³ and Singapore¹⁴ estimated a rate of 2.7, 2.8 and 7.9 per 10,000 patient admissions, respectively. However, most of their cases were identified on clinical grounds with confirmatory tests performed in the minority. Conversely, all our patients had DVTs confirmed on duplex ultrasound examination. If patients who had DVT diagnosed based on clinical features alone were also included, we expect the incidence of acute DVT in our hospital to be higher than 15.8 per 10,000 admissions. Notwithstanding differences in patient characteristics and admission policies, we believe that the rate of DVT is likely to be increasing among Asians. Part of this rising trend may be related to an ageing population, greater number of patients undergoing surgical procedures and suffering from malignant conditions. However, this figure is still considerably lower than the 0.9% reported in the Worcester study.² More importantly, almost 10% of our patients developed PE, a potentially fatal complication.

Similar to Caucasian populations, most of our patients had predisposing factors for DVT. The major risk factors for developing DVT in our patients were that of immobilisation, surgery and malignancy. These were also major risk factors in Caucasian populations.³ The female preponderance may reflect on unique conditions affecting women, such as breast and gynaecological malignancies and pelvic operations. However, the reason for the higher rate among Indians is unclear and requires further investigation.

Abdominal and pelvic surgical procedures accounted for more than half of surgery-related DVTs. A good proportion of these surgery-related DVTs could have been prevented if perioperative DVT prophylaxis was given.^{15,16} It is interesting to note that patients with surgically-related DVT had more intrinsic risk factors predisposing to DVT than patients who did not have any surgery.

The interpretation of data on thrombophilia here is limited by the retrospective nature of this study. The 4 tests most frequently encountered in this study are antithrombin, protein C and protein S levels, and anticardiolipin antibodies. Nonetheless, it is interesting to note that 20% of surgical patients, who were screened for underlying thrombophilic states, yielded positive results. In these cases, surgery may be the event that unmasked the underlying thrombophilic diseases, and these would be missed if surgery were assumed to be the sole cause of the DVT. Further studies on thrombophilia in our population are required for better understanding and more efficient screening of these conditions.

The risk stratification for DVT depends on the patient population base. A study based on a population of younger patients will naturally select genetically-related risk factors. No such study has been done on Asian populations. This study which is based on hospital patients exposed an older

cohort of patients bringing with them more of the problems of advancing age and less of inherited risk factors. Nonetheless, it gives an indication of the magnitude of the problem and suggests that DVT is an increasingly important condition in this region. In conclusion, this study shows that VTE is a common problem here. Major risk factors were identified and thromboprophylaxis should be seriously considered for patients at risk. Further prospective studies for better understanding of VTE in the Asian and Oriental populations are required.

REFERENCES

1. Scottish Intercollegiate Guidelines Network (SIGN). Prophylaxis of venous thromboembolism. Edinburgh: SIGN, 1995. SIGN Publication No. 2.
2. Anderson F A, Wheeler H B Jr, Goldberg R J, Hosmer D W, Patwardhan N A, Jovanovic B, et al. A population-based perspective of the incidence and case-fatality rates of venous thrombosis and pulmonary embolism: The Worcester DVT study. *Arch Intern Med* 1991; 151:933-8.
3. Geerts W H, Heit J A, Clagett G P, Pineo G F, Colwell C W, Anderson F A, et al. Sixth ACCP Consensus Conference on Antithrombotic Therapy. Prevention of venous thromboembolism. *Chest* 2001; 119(Suppl):132S-75S.
4. Hwang W S. The rarity of pulmonary thromboembolism in Asians. *Singapore Med J* 1968; 9:276-9.
5. Tinckler L F. Absence of pulmonary embolism in Asians [letter to editor]. *BMJ* 1964; i:50.
6. Shen M C, Lin J S, Tsay W. High prevalence of antithrombin III, protein C, protein S deficiency, but no Factor V Leiden mutation in venous thrombophilic Chinese patients in Taiwan. *Thromb Res* 1997; 87:377-85.
7. Lin J S, Shen M C, Tsay W. The Mutation at position 20210 in the 3'-untranslated region at the prothrombin gene is extremely rare in Taiwanese Chinese patients with venous thrombosis [letter]. *Thromb Haemost* 1998; 80:343.
8. Lim L C, Tan H H, Lee L H, Tien S L, Abdul Ghafar A. Activated protein C resistance: A study among 60 thromboembolic patients in the Singapore population. *Ann Acad Med Singapore* 1999; 28:252-5.
9. Lau G. Pulmonary thromboembolism in not uncommon — results and implications of a 5-year study of 116 necropsies. *Ann Acad Med Singapore* 1995; 24:356-65.
10. Teo C E S. A study of coroner's cases from hospitals: a comparison of autopsy and clinical diagnosis. *Ann Acad Med Singapore* 1993; 22: 4-7.
11. Chen L H, Yeong C T, Yeo G S H. Three cases of fatal pulmonary embolism in obstetrics. *Ann Acad Med Singapore* 1997; 26:356-9.
12. Woo K S, Mak G Y, Sung J Y, Woo J L, Metreweli C, Owen V. The incidence and clinical pattern of deep vein thrombosis in the Chinese in Hong Kong. *Singapore Med J* 1988; 29:357-9.
13. Liam C K, Ng S C. A review of patients with deep vein thrombosis diagnosed at University Hospital, Kuala Lumpur. *Ann Acad Med Singapore* 1990; 19:837-40.
14. Kueh Y K, Wang T L, Teo C P, Tan Y O. Acute deep vein thrombosis in hospitals practice. *Ann Acad Med Singapore* 1992; 21:345-8.
15. Ruban P, Yeo S J, Seow K H, Tan S K, Ng S C K. Deep vein thrombosis after total knee replacement. *Ann Acad Med Singapore* 2000; 29: 428-33.
16. Ho Y H, Seow-Choen F, Leong A, Eu K W, Nyam D, Teoh M K. Randomised, controlled trial of low molecular weight heparin vs no deep vein thrombosis prophylaxis for major colon and rectal surgery in Asian patients. *Dis Colon Rectum* 2000; 42:196-203.