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Symptomatic venous thromboembolism in Hong Kong Chinese children

香港華裔兒童所患的症狀性靜脈血栓塞

Objective. To determine the incidence of venous thromboembolic disease in children of Chinese origin, and associated predisposing factors.

Design. Retrospective case series.

Setting. A general, public hospital serving a population of approximately 181 000 children in Hong Kong.

Patients and methods. Hong Kong Chinese children under the age of 15 years who were diagnosed with a symptomatic venous thromboembolic event between 1995 and 2000 were included. Data on clinical features, predisposing factors, treatment, and outcome were obtained from review of hospital medical records.

Results. Eight children (five girls and three boys) of mean age 11.5 years (range, 0-14.7 years) were included in the study. They presented with deep vein thrombosis (n=4, with pulmonary embolism in one), superior vena cava thrombosis (n=1), and cerebral venous sinus thrombosis (n=3). Predisposing factors included hereditary protein C deficiency (n=3), protein S deficiency (n=2), anticardiolipin antibodies (n=1), malignancy (n=3), recent neurosurgery (n=2), infection (n=1), with multiple predisposing factors seen in three patients. Anticoagulant therapy was prescribed in five patients, and long-term warfarin therapy was required in two cases. Venous thromboembolic disease resolved in all children, but one patient had a recurrence after cessation of warfarin therapy, and one patient had post-thrombotic syndrome.

Conclusion. The rate of venous thromboembolic disease in Hong Kong Chinese children was comparable to that seen in Caucasian children, with an annual incidence of 0.74 per 100 000 children. Predisposing factors, including hereditary prothrombotic conditions, were common.

Key words:

Child;
Hong Kong;
Risk factors;
Thromboembolism;
Venous thrombosis

關鍵詞：

兒童；
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目的：確定華裔兒童的靜脈血栓塞病發率和致病誘因。

設計：病例系列回顧。

安排：香港一所公營醫院，負責地區上大約 181 000 兒童人口的醫療服務。

患者及方法：研究對象為在 1995 年至 2000 年期間，被診斷患上症狀性靜脈血栓塞的 15 歲以下香港華裔兒童。本研究通過檢視醫院的病歷紀錄，得出臨床特徵、致病誘因、治療和結果的資料。

結果：8 名病童(5 女 3 男)的年齡中位數為 11.5 歲(分佈域：0-14.7 歲)，他們分別患有深層靜脈血栓形成(4 人，其中一位伴有肺栓塞)，上腔靜脈血栓形成(1 人)，腦靜脈竇血栓形成(3 人)。致病誘因則包括遺傳性蛋白 C 缺乏(3 人)、蛋白 S 缺乏(2 人)、抗心磷脂抗體(1 人)、惡性腫瘤(3 人)、近期曾作神經外科治療(2 人)、感染(1 人)，其中 3 人出現多種致病誘因的症狀。病童中有 5 人曾接受抗凝劑治療，其中兩人需長期接受華法林療法。所有病童已康復，但其中 1 人在停止華法林療法後復發，另有 1 人則出現後血栓症的症狀。

結論：香港華裔兒童靜脈血栓塞的病發率和白人兒童的病發率相似，年病發率大約為每 10 萬兒童中有 0.74 人患病。一些致病誘因常見於患者，包括遺傳性凝血酶原疾病。

Introduction

Venous thromboembolism (VTE) is primarily a disease of adults, and Chinese people are much less frequently affected than Caucasians.^{1,2} With improvements in diagnostic facilities and the increasing complexity of medical care, the occurrence of VTE in children has become a focus of concern in North America

and Europe. The establishment of national registries has helped to confirm that VTE in children is not uncommon, and that specific predisposing factors differ from those seen in adult patients.^{3,4} Similar studies in Chinese children are lacking. This study aimed to delineate the frequency and risk factors associated with VTE among Chinese children in Hong Kong.

Patients and methods

Children under the care of Tuen Mun Hospital between January 1995 and December 2000, with a diagnosis of deep venous thrombosis and embolism, or cerebral venous sinus thrombosis on recommended imaging studies,⁵ were recruited. Only patients of ethnic Chinese origin were included. Hospital charts were reviewed retrospectively to gather data on clinical features, predisposing factors, diagnostic evaluation completed, antithrombotic therapy given, and outcome. The use of prolonged prophylaxis, recurrence of thrombosis, and residual complications were assessed in December 2002. A thrombophilic condition was considered hereditary, if the laboratory abnormality persisted after recovery from the primary event and cessation of anticoagulant treatment, or if the same condition was detected in a first-degree relative.

Results

Eight Chinese children, three boys and five girls, were identified during the study period. Their ages ranged from 15 days to 14.7 years (mean, 11.5 years), with seven aged over 11 years. The clinical presentation, predisposing factors, treatment, and outcomes are summarised in the Table.

Cerebral venous sinus thrombosis occurred in three (38%) cases, and was associated with multiple cerebral and cerebellar infarctions in one patient. Seizures were the presenting symptom in all patients, and the diagnosis was confirmed on magnetic resonance angiography. Peripheral deep vein thrombosis (DVT) occurred in four (50%) patients, involving the lower limbs unilaterally, with typical signs of inflammation and swelling. Doppler ultrasonography established the diagnosis of DVT in these cases. Extensive inferior vena cava thrombosis, revealed by venography, also occurred in one of these four patients. Symptomatic pulmonary embolism, shown on ventilation-perfusion scanning, was seen in another of the four. The remaining patient presented with superior vena cava thrombosis as a result of disseminated Wilms tumour, with considerable mediastinal involvement. This diagnosis was made following computed tomography scans of the chest, and the case has been reported elsewhere.⁶ All patients with the exception of the patient with disseminated Wilms tumour were tested for hereditary prothrombotic conditions, including antithrombin III, protein C, protein S, and activated protein C resistance. Heterozygous protein C deficiency was found in three (43%) patients, and heterozygous protein S deficiency was found in two (29%) patients. Of these five patients with hereditary thrombophilia, three had concurrent medical conditions or treatment that rendered them vulnerable to venous thrombosis. These included malignancy, recent neurosurgery, and treatment with L-asparaginase. Of the remaining two patients in whom hereditary thrombophilia was not detected, acquired abnormalities known to be associated with VTE were found. One had anticardiolipin antibodies, and the other was a neonate suffering from infected cephalhaematoma, with underlying osteomyelitis of the parietal bone by *Escherichia coli*. The latter patient has been reported elsewhere.⁷

Table. Summary of clinical and laboratory features in children with venous thromboembolism (n=8)

Case No.	Sex/Age (years)	Venous thromboembolic events	Hereditary prothrombotic factors	Other predisposing factors	Treatment and outcome
1	M/12.2	Bilateral cerebral infarction; thrombosis of straight sinuses and the vein of Galen	Hereditary PC* deficiency	Nil	Unfractionated heparin followed by long-term warfarin; tetraplegic
2	F/14.4	DVT† in right lower limb; symptomatic pulmonary embolism	Normal AT III‡, PC, PS§, and APCR¶	Anticardiolipin immunoglobulin M present	Unfractionated heparin followed by long-term warfarin; post-thrombotic syndrome
3	F/11.8	DVT in right lower limb	Hereditary PS deficiency	Nil	Enoxaparin followed by short-term warfarin
4	F/11.8	DVT in left lower limb	Hereditary PS deficiency	Recent neurosurgery	Fresh frozen plasma followed by enoxaparin and long-term warfarin
5	M/14.3	Thrombosis in right transverse and sigmoid sinuses	Hereditary PC deficiency	Brain tumour; recent neurosurgery	No treatment
6	F/15 days	Thrombosis in left transverse sinus	Normal AT III, PC, PS, and APCR	Infected cephalhaematoma	No treatment
7	F/14.7	Superior vena cava thrombosis	Not tested	Disseminated Wilms tumour	Resolved with combination chemotherapy
8	M/12.6	DVT in left lower limb	Hereditary PC deficiency	Acute leukaemia; L-asparaginase therapy	Enoxaparin followed by short-term warfarin; recurrence in the right lower limb; on long-term warfarin

* PC protein C

† DVT deep vein thrombosis

‡ AT III antithrombin III

§ PS protein S

¶ APCR activated protein C resistance

Five patients were treated initially with either unfractionated or low-molecular-weight heparin, followed by warfarin treatment. The use of anticoagulant therapy was delayed by 3 weeks in the patient with hereditary protein S deficiency (patient 4). This patient developed DVT shortly after excision of an intracranial arteriovenous malformation and intracerebral bleeding,⁸ and received treatment with fresh frozen plasma to maintain a protein S level of 30 U/mL. Long-term warfarin treatment was recommended for this patient. It was also used in another patient (patient 8) with recurrent DVT after cessation of warfarin treatment. Three patients were not treated with anticoagulants. For the neonatal patient (patient 6) with sinovenous thrombosis, anticoagulant therapy was not given, but the thrombosis resolved after aggressive treatment of the underlying bacterial infection. Anticoagulant therapy was not given to patient 5, who had sinovenous thrombosis after surgery for a hypothalamic pilocytic astrocytoma, because the risk of bleeding was considered to outweigh the potential benefits of treatment. The thrombus resolved subsequently. In the patient with superior vena cava thrombosis due to disseminated Wilms tumour, the condition resolved rapidly after initiation of chemotherapy. Six patients, with a mean follow-up of 4.2 years (range, 2.1-8.0 years), had complete clinical recovery with respect to their venous thromboembolic illness. Patient 1 had severe neurological sequelae and remained tetraplegic. Patient 2 developed post-thrombotic syndrome, with fluctuating venous stasis and dermatitis in the involved limb.

Discussion

This study represents the first case series of VTE among Chinese children in Hong Kong. As Tuen Mun Hospital is the sole hospital serving a population of 181 000 children under the age of 15 years in the Tuen Mun and Yuen Long areas,⁹ the eight patients reported indicate an annual incidence of VTE of 0.74 per 100 000 children. The proportion of non-Chinese children within the districts was unavailable, but 6% of children admitted to Tuen Mun Hospital annually are non-Chinese (unpublished data). For this reason, and the probability of underdiagnosis in a retrospective series, the actual annual incidence rate is likely to be higher. Despite these limitations, the observed incidence was close to figures in Caucasian populations registered prospectively. The Canadian Registry has reported an annual incidence of 0.7 per 100 000 children,³ while the Dutch Registry noted an incidence of 1.4 per 100 000.⁴ The latter figure, however, included asymptomatic cases, and both registries included patients aged up to 18 years. Adjusting these figures to exclude asymptomatic cases and children aged 15 years or above, the Canadian and Dutch incidence rates would be 0.54 and 0.83 per 100 000, respectively. The approximation to the rate of VTE in Caucasian populations seen in the present series is in marked contrast to the data seen for adults. The incidence of VTE among local Chinese has been reported as less than one tenth of Caucasian figures.^{1,2}

There are two particular reasons why the incidence rate identified in this study may be an underestimate. Firstly, there is a deficiency of cases of catheter-associated thrombosis in this series, given that the use of a central venous catheter is a common risk factor for VTE in newborn infants and older children.^{3,4,10} The condition may have been underdiagnosed because of a lack of awareness. Secondly, there appears to be a notable absence of patients with congenital heart disease in the series, as VTE is not uncommon in these patients, especially after interventional or surgical procedures.¹¹ As all patients with serious congenital heart disease at Tuen Mun Hospital are referred to the paediatric cardiac centre on Hong Kong Island, VTE among these patients would not have been managed in our hospital.

Children are much less susceptible to VTE compared with adults, and the commonly associated predisposing factors also differ (Box).^{12,13} For example, medical illnesses, such as stroke and heart failure resulting in prolonged immobilisation; orthopaedic surgery on the hips, knees or spine; malignancies; and intravenous substance abuse have been reported as the most frequent underlying conditions found in adults with VTE.² These conditions are rarely encountered in the paediatric population. Even within the adult population, advanced age is a strong determinant, with the majority of cases occurring in patients over the age of 50 years.^{2,12} Therefore, it is not surprising that the pattern of VTE in children in differing ethnic groups is distinct from that in comparable adult populations.

Hereditary prothrombotic conditions, including protein C and protein S deficiencies, predominated in our series. Such conditions have also been shown to be important in Caucasian children but the pattern of prothrombotic derangement seen was different.¹³ Factor V Leiden (or factor V R506Q mutation) has been noted as the most frequent thrombophilic condition among Caucasian patients with venous thrombosis.¹³ Using activated protein C resistance as a surrogate marker for this mutation, however, we were unable to document any case in the seven patients tested in the current series. Indeed, factor V Leiden, and the recently described hereditary prothrombotic conditions, such as prothrombin G20210A mutation, are rarely seen in Chinese.^{14,15} It is important that such a long-lasting prothrombotic condition in a child with VTE is not missed because the risk of recurrence is substantial. As most

Common predisposing factors for childhood venous thromboembolism^{3,4,10}

Hereditary disorders

Genetic defects in procoagulants or their inhibitors
eg antithrombin III, protein C, protein S, factor V Leiden

Interventional procedures

Central venous catheterization

Surgery

Acquired hypercoagulable states

Cancer

Congenital heart disease

Trauma

Infection

Nephrotic syndrome

of these conditions have a dominant pattern of inheritance, other family members also need to be informed and screened for similar defects.

Although malignancy was noted in three patients in this series, it was only considered to be directly responsible for VTE in the patient with superior vena cava thrombosis, probably as a result of tumour compression and invasion.⁶ In the other two patients, multiple predisposing factors were present. Both patients had hereditary protein C deficiencies. Neurosurgery, a well-documented procedure associated with increased coagulability,¹⁶ was an important likely contributing factor in the patient with brain tumour. Treatment with *E coli* L-asparaginase, another well-described risk factor for thrombosis,¹⁷ had been given to the other patient just prior to the appearance of DVT.

Newborn infants represent a special group of patients in which VTE may occur.¹⁰ Infections, asphyxia, polycythaemia, and hypovolaemia are common risk factors, but the majority of neonatal cases of VTE are associated with the use of central venous catheters.^{4,10} Data from prospective and rigorous monitoring showed that arterial and venous thrombosis occurred at a rate of 2.4 per 1000 neonatal admissions,¹⁰ or 1.6 per 1000 admissions if only venous thrombosis was considered. Part of the reason for the higher rate of detection in this age-group may relate to the pattern of care and monitoring of sick neonates. Indeed, 32 of the 47 cases of neonatal thrombosis registered in the Dutch report were asymptomatic.⁴ Thus, direct comparison of reported statistics from different institutions is difficult in the absence of uniform case definitions. The treatment of VTE in children follows that of adults, and the use of anticoagulants remains the mainstay of treatment.^{5,18} Bleeding remains the most important complication of medical therapy, and this risk must be balanced against the potential benefits of treatment. In the newborn infant, however, this risk-benefit ratio is largely unknown and most physicians prefer aggressive treatment of the predisposing condition.¹⁰ Long-term follow-up is necessary to monitor for recurrence of VTE, and complications, such as post-thrombotic syndrome.¹⁹ However, reports of series including paediatric cases in the medical literature are limited.²⁰

Conclusion

Symptomatic VTE remains an uncommon clinical entity in Chinese children, but occurs at a comparable rate to that seen in Caucasian children. Predisposing factors are usually present, and are often multiple in number. A search for hereditary prothrombotic conditions is indicated in order to guide long-term management and family counselling.²¹ Territorywide and prospective surveillance in Hong Kong is required if the true incidence of VTE in children is to be determined.

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