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Aleena Zia

Aga Khan University Hospital Karachi, Pakistan

Mohammad Wasay

Aga Khan University, Karachi

Subash Kaul

Nizam Institute of Medical Sciences, Hyderabad, India.

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EPIDEMIOLOGY OF CEREBRAL VENOUS THROMBOSIS IN ASIAN COUNTRIES

Aleena Zia¹, Mohammad Wasay¹, Subash Kaul²

¹ Medical College, Department of Medicine, Aga Khan University, Karachi.

² Nizam Institute of Medical Sciences, Hyderabad, India.

Correspondence to: Mohammad Wasay MD, FRCP, FAAN, Professor, Department of Neurology, Aga Khan University, Stadium Road, Karachi 74800, Pakistan.

Email: mohammad.wasay@aku.edu

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INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare form of venous thromboembolism (VTE). CVT represents almost 0.5% -3% of all the types of stroke, affecting predominantly younger people, with an estimated incidence for adults of 3-4 per million, and for children 7 per million. In the pre-antibiotics era, the leading cause of CVT were septic processes, currently, the aseptic form of CVT predominates. ⁽¹⁾ About 75% of all adult patients are women, over the past decade, advances in neuroimaging and treatments have significantly improved the disease's prognosis with 80% of sufferers having a good neurological outcome. ⁽²⁾ The largest source of international data on the condition, the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), included 624 patients and reported that 50% of these cases were related to Oral contraceptive pills (OCP), 6% were due to pregnancy and 14% were secondary to puerperium and while looking at the different outcomes found that 356 patients (57.1%) had no symptom or signs, 137 (22%) had minor residual symptoms, and 47 (7.5%) had mild impairments, Eighteen (2.9%) were moderately impaired, 14 (2.2%) were severely handicapped, and 52 (8.3%) had died at the end of follow up (median 16 months)⁽³⁾. While there is a plethora of research available over the different aspects of CVT internationally, there is a relative paucity of information when focusing on Asia.

OBJECTIVE

This review is aimed at gathering and analyzing information from research conducted from different countries in Asian countries and summarizes the overall epidemiology, risk factors, treatment options and challenges of CVT seen in Asia.

METHODS

An extensive literature search was conducted first using the terms CVT in Asia and then looking at individual Asian countries. The countries included in the search comprised of Japan, Thailand, Singapore, Indonesia, Malaysia, Korea, China, India, Pakistan, Israel, Saudi Arabia and Kuwait. Only registries or case series' with greater than 20 cases were reviewed. The search query cerebral venous thrombosis within Asia yielded 108 results, after reviewing them for relevance and substance, 16 articles from all over Asia were included in this review.

Incidence

There is a dearth of population based incidence surveys related to CVT in most Asian countries. A prospective population based survey conducted in the Isfahan region of Iran, between 2001-04, found the annual incidence of CVT to be 12.1 per million people ⁽⁴⁾.

Age

CVT has always been considered a disease of young people. A study, which included 109 CVT patients from Dubai and Karachi between the years 1991 and 2007, found the median age of the patients to be 35 (mean, 35.8); the females were 5 years younger than the males; mean age of women, 33.2; mean age of men, 38.7 years. ⁽⁵⁾ The mean age of CVT sufferers was found to be 35.5 years; [36.3 in men and 35.3 in women] in an Iranian study mentioned above, which recorded a total of 1122 patients. ⁽⁴⁾ An Indian study conducted between 2002 and 2010 in Hyderabad, which included 428 people. found that the mean age of presentation was 31.3 years ⁽⁶⁾, similar results were obtained by Pai et al who found that the mean age of their population of 612 people was 31.9 years A large multi centred study which included 204 women who suffered from CVT from India, Pakistan, Sri Lanka, Syria, Thailand, Singapore, Turkey and Iran found that the mean age of presentation was 29.0 years ⁽⁷⁾. The mean age reported by Misra et al in their RCT comprising of 66 patients from India was 34.5 years ⁽⁸⁾. Pongvarin et al reported a mean age of 36.6 years in their study population ⁽⁹⁾. When comparing this Asian data with the findings of the ISCVT, we can see that the mean age of onset is significantly lower in our population as compared to the European population studied, the main age of presentation of the 628 patients enrolled in

the study being 39.1 and median being 37.0 years⁽³⁾

Gender

CVT has traditionally been thought to predominate amongst women. A study that included patients from Pakistan and the Middle East found the division of their patients to be 53.0% women and 47.0% men⁽⁵⁾. Janghorbani et al found that out of 122 patients with CVT in Isfahan, 26 (21.3%) were men and 96 (78.7%) were women.⁽⁴⁾ However, an Indian study reported that of its 428 CVT patients, 53.7% were men and 46.3% were women⁽⁶⁾. Misra et al studied 66 patients with CVT and reported that 62.1% of their study population were women, and 37.9% were men, further demonstrating a female predominance towards the condition⁽⁸⁾. Pongvarin et al reviewed 194 patients with CVT in Thailand between 1993 and 2005 and found that 127 (65.5%) were women⁽⁹⁾. When comparing this information with the results of the ISCVT, where 74.5% of CVT patients were female and 25.5% male⁽³⁾, we can see that our data is generally consistent with international trends when looking at gender distribution.

CVT in Children

CVT in children is a result of complex multifactorial elements which result in a prothrombotic state, usually arising from the interaction of acute and chronic pathologies⁽¹⁰⁾. Janghorbani et al reported a total of 3 cases per a population of 227, 941 people in the 15-19 age group⁽⁴⁾. An Indian study conducted between 2001 and 2010 reported that 39 of its 624 CVT patients were children (11). Ozbek et al looked at a 122 pediatric patients of venous thrombosis in Ankara, Turkey and found that 28 (22.9%) had CVT. 54% of all thrombotic patients had an inherited form of hypercoagulability, the most common being MTHFR 677C-T mutation with factor V Leiden coming in second.⁽¹²⁾

Risk Factors

There are several risk factors for CVT, including both modifiable and non modifiable. The most significant non modifiable risk factor would be female gender as noted by literature from Pakistan, Iran and the Middle East⁽⁵⁾⁽⁷⁾⁽¹³⁾. This female predisposition has largely been attributed to the risk factors of puerperium and oral contraceptive pill use⁽⁵⁾⁽⁷⁾⁽⁶⁾. Another significant risk factor would be hypercoagulability due to inherited or acquired thrombophilia, deficiencies of protein C, S or antithrombin III, hyperhomocysteinemia, or presence of anti-phospholipid or anti cardiolipin antibodies as demonstrated by several studies undertaken in Pakistan, India, the Middle East and Japan⁽⁵⁾⁽⁶⁾⁽⁷⁾⁽¹¹⁾⁽¹⁴⁾⁽¹⁵⁾. Infections have also been demonstrated as a significant risk factor towards the development of CVT⁽⁵⁾⁽⁷⁾⁽¹⁵⁾. Other risk factors demonstrated include anemia and alcoholism⁽⁶⁾⁽⁷⁾⁽¹⁴⁾. Patil et al reported dehydration to be a risk factor precipitating CVT in their review of 50 patients in a tertiary care setting in India.⁽¹⁶⁾

Daif et al identified Behcet's disease as a significant risk factor for the development of CVT in their series of 40 patients in the Saudi population, with 10 of the 40 CVT patients (25%) suffering from Behcet's disease, they also found that 3 of their 40 patients (7.5%) suffered from intracranial tumors.⁽¹⁵⁾ Al Hashel et al, in their retrospective review of 110 patients in Kuwait, found that 10 of the CVT patients also suffered from Behcet's disease (9.1%), demonstrating this particular risk factor specific to the Arab population.⁽¹⁷⁾ When comparing our findings to the results of the ISCVT, we found that several risk factors overlapped. 34.1% of cases were identified to have thrombophilias, congenital or acquired. 5.9% had antiphospholipid antibodies present. 4.5% had hyperhomocysteinemia. Other risk factors identified that correlated with our data include anemia (9.2%), infection (12.3%), pregnancy (6.3%), puerperium (13.8%), use of oral contraceptive pills (54.3%) and malignancy (7.4%). A significant risk factors identified in the ISCVT that we did not see in our literature were mechanical precipitants including trauma, LPs, or a jugular catheter (4.5%)⁽³⁾

Treatment

The mainstay of therapy in acute and sub acute CVT is anticoagulation. There are several rationales for anticoagulation therapy in CVT: To prevent thrombus growth, to facilitate recanalization, and to prevent DVT or PE⁽¹⁸⁾. A study in Iran that included 122 patients reported that all were anticoagulated; Thirty-two patients (26.2%) were anticoagulated with heparin only, 75 (61.5%) patients treated with heparin and anticonvulsive drugs, 8 (6.6%) patients treated with low molecular weight heparin and 7 (5.7%) patients treated with heparin plus antibiotics (4). Similarly, in a study conducted in Pakistan and the Middle East; 73 of 109 (67%) received acute anticoagulation, 10 (9%) received low-dose subcutaneous heparin for deep venous thrombosis prophylaxis and 10 (9%) received antiplatelet agents. None of the patients underwent thrombolysis. Antibiotics were administered to 28 (26%) of the patients. 4 of these underwent neurosurgical intervention (frontal lobectomy in 2, hematoma evacuation in 1, and ventriculoperitoneal shunt in 1). Thirteen patients received steroids, 7 received mannitol, and 3 received acetazolamide⁽⁵⁾. In an Indian study, similar treatment methods were reported; 396 (92.5%) patients received unfractionated heparin for 7 days overlapping with oral anticoagulants for 3 days which was continued for a minimum period of 6 months. LMWH was given in 41 (9.5%) of patients, who had massive hemorrhagic infarcts with midline shift. Six patients (1.4%) not showing a satisfactory response to unfractionated heparin were administered intrasinus urokinase under catheter guidance via the trans femoral route. Decompression craniotomy was done in 16 (3.7%) patients⁽⁶⁾. In another study conducted amongst women

Table 1. studies conducted in Asian countries

#	Country	Author	No of Patients	Male/ Female	Risk Factors	Treatment	Outcome
1	India	Narayan et al	428	M=53.7% F= 46.3%	Anemia(18.4%) Hyperhomocysteineimiamia (18.2%) Alcoholism (15.6%) Protein S deficiency (12.3%) OCP use (11.4%)	UFH (92.5%) LMWH (9.5%) Intravenous urokinase (1.4%) Decompression craniotomy (3.7%)	Death (7.7%) Functionally dependent (25.7%) Functionally independent mRS = 2 (10.9%) Complete recovery (52.8%)
2	Pakistan and UAE	Khealani et al	109	M = 47% F = 53%	Infection (18%) Postpartum state (17%), Hyperhomocystinemia(9%) Genetic thrombophilia (5%) Oral contraceptive pill use (3%)	Acute anticoagulation (67%) Low dose subcutaneous agents (9%) Anti platelet agents (9%) Antibiotics	Death (9%) Functionally dependent (7%) Functionally independent (56%)
3	Saudi Arabia	Daif et al	40	M = 50% F = 50%	Behçet's disease (25%) Antiphospholipid antibodies (10%) Protein S deficiency (7.5%) Intracranial tumors(7.5%) SLE (7.5%)	Repeated LPs (27.5%) Steroids/acetazolamide (20%) Heparin (10%)	Death (10%) Functionally dependent/disabled (17.5%) Complete recovery (72%)
4	Kuwait	Al Hashel et al	110	M = 37.3% F = 62.7%	Behcet's disease (9%)	UFH (50%) LMWH (27%) Warfarin (18%)	
5	Japan	Shindo et al	22		Congenital thrombophilia		Poor prognosis (mRS 3-5)

from 8 different Asian countries including India, Pakistan, Sri Lanka, Iran, Thailand, Turkey and Syria found that anticoagulation was the most frequent treatment, used in 122 patients (61%), and followed by antiplatelet therapy in 75 patients (37%). Three patients (1.5%) underwent surgical decompression. No patients received thrombolytic therapy⁽⁷⁾. Daif et al reported treating 11 (27.5%) patients by repeated lumbar puncture. Steroids and/or acetazolamide were used in 8 (20%) patients. 4 (10%) patients were treated with heparin (15). Misra et al compared the safety and efficacy of LMWH to unfractionated heparin in a randomized control trial with 32 people receiving unfractionated heparin and 34 receiving LMWH. Baseline characteristics were similar between the two groups, 6 patients died, all of them belonging to the unfractionated heparin group. At 3 months' follow up 30 patients in the LMWH group had recovered completely as opposed to 20 in the unfractionated group, one patient had to have therapy withdrawn from the unfractionated group due to heparin induced thrombosis, these results indicate the superiority of LMWH over unfractionated heparin in terms of outcomes⁽¹⁶⁾. When comparing this to the ISCVT, we find marked similarities, in their population 520 or (83.3%) of patients were anticoagulated with intravenous heparin (401 cases [64%]) or subcutaneous low-molecular-weight heparin (LMWH) (218 patients [34.9%]). A few patients received only subcutaneous LMWH in prophylactic dosage 9 patients (1.4%) or antiplatelet drugs 37 patients (5.9%). Thirteen patients (2.1%) were treated with local endovascular thrombolysis. Additional treatments included antiepileptic drugs 277 patients (44.4%), osmotherapy 82 (13.2%), steroids 150 (24.1%), acetazolamide 61 (9.8%), and diuretics 34 (5.5%). Shunts were performed in 10 patients (1.6%), 9 (1.4%) had decompressive craniotomy or hematoma evacuation⁽³⁾.

Outcome

Outcomes for CVT, like other forms of stroke vary. Khealani et al found that of their 109 patients, fifty were either dead ($n = 7$) or disabled with a modified Rankin score of greater than 2 ($n = 43$) (5). Khan et al looked at 110 women with pregnancy related strokes from Pakistan, India, Iran, Sri Lanka and Turkey found that of patients with CVT, 14.3% at a modified Rankin score of greater than 3 at a 30 day follow up (19). Narayan et al found that of their 428 patients, 33 (7.7%) died during their hospital stay, 90 days' follow up was available for 416 patients, of these 226 (52.8%) were normal with a mRS of 0 to 1, 47 (10.9%) had become functionally independent with a mRS of 2, and 110 (25.7%) were functionally dependent with a mRS of 3 to 5⁽⁶⁾. Pongvarin et al reported that 51 of their 194 patients (26.3%) had a mRS of 3 to 6 with poor outcomes, with an overall mortality rate of 8.4%. They were able to identify certain factors that determined the nature of the outcome.

Poor outcomes were associated with malignancy, low GCS and presence of hemorrhagic infarction. The involvement of the lateral sinus was associated with good outcomes⁽⁹⁾. Pai et al reported a mortality of 12.9% in their population of 612 adults and children, 18.3% were reported as being wheelchair bound or functionally dependant, 35.5% had varying degrees of disability and 23.3% had recovered completely at a one year follow up with 5 cases being lost to follow up⁽¹¹⁾. When comparing this to the findings of the ISCVT, several similarities can be appreciated. Of the 624 adult patients enrolled in the study, 356 (57.8%) had no symptoms at the end of follow up (median 16 months), 137 (22%) had minor residual symptoms with a mRS of 1 and 47 (7.5%) had mild impairment with a mRS of 2. 18 (2.9%) were moderately impaired with a mRS of 3, 14 (2.2%) were severely handicapped with a mRS of 4 or 5 and 52 (8.3%) had died.

CHALLENGES AND FUTURE DIRECTION

One of the greatest challenges posed during this review was the paucity of representative data from the Asian region, with only one country having reliable epidemiological data of CVT by virtue of setting up a registry. There is also dearth of literature available when focusing specifically on CVT in children even though it has shown to affect them as well and is traditionally referred to as an illness of children and young people. CVT is a significant cause of stroke in the young Asian population so it would be prudent to establish better systems of recording its frequency, course and outcomes.

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Author's Contribution:

Dr. Wasay: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review

Dr. Aleena Zia: Data collection, data analysis, manuscript writing, manuscript review

Dr. Subash kaul: Data analysis, manuscript writing, manuscript review