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Review

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Stroke in Asia

Kay Sin Tan[a] Jeyaraj Durai Pandian[b] Liping Liu[c] Kazunori Toyoda[d] Thomas Wai Hon Leung[e] Shinichiro Uchiyama[f] Sathoshi Kuroda[g] Nijasri C. Suwanwela[h] Sanjith Aaron[i] Hui Meng Chang[j] Narayanaswamy Venketasubramanian[k]

[a]Division of Neurology, Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [b]Department of Neurology, Christian Medical College, Ludhiana, India; [c]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; [d]National Cerebral and Cardiovascular Center, Suita, Japan; [e]Department of Medicine and Therapeutics, Faculty of Medicine, The Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China; [f]Centre for Brain and Cerebral Vessels, Sanno Medical Centre, International University of Health and Welfare, Tokyo, Japan; [g]Department of Neurosurgery, Toyama University, Toyama, Japan; [h]Chulalongkorn Stroke Centre, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [i]Department of Medicine, Christian Medical College, Vellore, India; [j]Department of Neurology, National Neuroscience Institute, Singapore General Hospital, Singapore, Singapore; [k]Raffles Neuroscience Centre, Raffles Hospital, Singapore, Singapore

Keywords

Classification · Stroke intervention · Stroke systems of care · Epidemiology · Aetiology · Asian stroke pattern

Abstract

Background: There is a significant burden of stroke in Asia. Asia has the largest population in the world in 2023, estimated at 4.7 billion. Approximately 9.5–10.6 million strokes will be anticipated annually in the backdrop of a diverse group of well-developed and less developed countries with large disparities in stroke care resources. In addition, Asian countries are in varying phases of epidemiological transition. ***Summary:*** In this review, we examined recent epidemiological features of ischaemic stroke and intracerebral haemorrhage in Asia with recent developments in hyperacute stroke reperfusion therapy and technical improvements in intracerebral haemorrhage. The article also discussed the spectrum of cerebrovascular diseases in Asia, which include intracranial atherosclerosis, intracerebral haemorrhage, infective aetiologies of stroke, moyamoya disease, vascular dissection, radiation vasculopathy, and cerebral venous thrombosis. ***Key Messages:*** The review of selected literature and recent updates calls for attention to the different requirements for resources within Asia and highlights the breadth of cerebrovascular diseases still requiring further research and more effective therapies.

Introduction

Stroke is a major cause of death and disability globally with significant burden of disease in Asia. Stroke in Asia has unique epidemiological features, which differ from other parts of the world [1–3]. Recent advances in hyperacute reperfusion therapy for acute ischaemic stroke (IS) have changed the practice of stroke in Asia. This progress has been augmented by the rapid adoption of

karger@karger.com
www.karger.com/cee

Correspondence to:
Kay Sin Tan, tanks18@hotmail.com

advanced imaging and interventional treatment with evidence from clinical trials on reperfusion therapy in hyperacute strokes particularly in major urban stroke centres. In the treatment of intracerebral haemorrhage (ICH), improvements in surgical access and medical management strategies have determined the direction of future therapy in this area [4, 5].

The purpose of this review article is to outline and expand upon key areas related to the spectrum of cerebrovascular diseases in Asia. It will summarize key epidemiological features of stroke in Asia including the prevalent stroke subtypes and examine the impact of chronic infection and infective aetiologies on cerebrovascular diseases. Cerebrovascular diseases more prevalent in Asia including moyamoya disease (MMD), radiation vasculopathies, and cerebral venous thrombosis (CVT) will be discussed in more detail under separate headings.

Stroke Epidemiology in Asia

Epidemiological studies on stroke in Asia have shown varying levels of mortality, incidence, prevalence, and burden of disease. Mortality rate is lowest in Japan at 43.3/100,000 person-years and Singapore 47.9/100,000 person-years and highest in Indonesia 193.3/100,000 person-years and Mongolia 222.6/100,000 person-years as shown in Table 1. Stroke incidence also showed significant variations from different studies [1]. Stroke incidence data are available for some countries in East Asia with the lowest rate observed in Malaysia (67/100,000 person-years). The highest rates were in Japan (422/100,000 person-years among men and 212/100,000 person-years among women). However, these results were not strictly comparable as the methods used were variable and the studies were performed at different time points [1]. Data on stroke prevalence may vary between different studies as the study methods used for case finding investigated using differing age bands.

The Global Burden of Disease study in 2019 showed that in Asia, the greatest stroke burden was in East and South-East Asia [2]. IS contributes to a higher proportion of strokes in South Asia compared to East and Southeast Asia.

Table 1. Age-sex standardized mortality due to stroke in Asia

Country	Age-sex standardized mortality/100, 000 person-years
Mongolia	222.6
Indonesia	193.3
Myanmar	165.4
DPR Korea	149.6
Lao PDR	141.3
Cambodia	137.8
China	126.9
Vietnam	124.5
Timor Leste	117.3
Philippines	109.6
Malaysia	84.3
Pakistan	83.3
India	82.4
South Korea	77.4
Nepal	73.5
Brunei	68.6
Sri Lanka	65.4
Thailand	62.8
Bhutan	58.3
Taiwan	56.8
Papua New Guinea	56.4
Bangladesh	54.8
Singapore	47.9
Japan	43.3

Epidemiology of IS in Asia

In Asia (2017), IS incidence was highest in China (155.7/100,000, 95% CI: 140.8–173.2) and North Korea (120.6/100,000, 95% CI: 107.6–135.9) and lowest in Bhutan (60.6/100,000, 95% CI: 53.4–69.4) and Thailand (62.4/100,000, 95% CI: 55.1–71.0) [3]. Overall, the burden of IS as measured by disability-adjusted life years (DALYs) differed between the various regions in East Asia, being highest in North Korea and lowest in Japan. In South Asia, Bangladesh and Bhutan have the highest and lowest DALYs while Papua New Guinea and Singapore in Southeast Asia occupy these positions for DALYs, respectively [3].

Stroke registries have reported that IS comprises 43.5% (Vietnam) to 76.1% (South Korea) of acute stroke admissions [1]. IS mechanisms based on TOAST criteria reported a range of frequencies without a clear regional pattern in hospital-based registries [6–17] as shown in Table 2. However, a systematic review reported a higher proportion of lacunar strokes among Chinese population compared to White population [18]. A greater proportion of large artery atherosclerosis have been reported in China, Korea, India, Pakistan, and Indonesia [6, 8, 11, 15] as shown in Table 2 and from a comparative study between 2 cohorts of IS and transient ischaemic attack (TIA) patients from Hong Kong and the UK [19]. Overall, large vessel and small vessel diseases appear to be more common stroke subtypes in Asia [20].

Table 2. IS subtypes based on registries

Country	Registry type	Year of publication	*N*	SVD, %	LAA, %	CE, %	Others, %	Unknown, %
East Asia								
China [6]	Hospital	2016	1,982	28.6	60.9	8.7		1.8
Japan [7]	Population	2010	1,389	54.1	21.0	22.9		2.0
Korea [8]	Hospital – multicentre	2020	39,291	19.9	32.6	21.3	3.7	22.5
Taiwan [9]	Hospital	2021	4,953	27.7	21.0	24.3	5.0	22.1
South Asia								
Bangladesh [10]	Hospital	2016	679	45.4	22.5	4.9		17.2
India [11]	Hospital – multicentre	2018	2066	14.2	29.2	24.9	3.4	27.6
Nepal [12]	Hospital	2015	56	46.4	17.9	35.7		
Pakistan [13]	Hospital – multicentre	2014	874	25.7	31.7	10.4		
Sri Lanka [14]	Hospital	2001	103	41				
Southeast Asia								
Indonesia [15]	Hospital	2018	235	26.7	59.6	2.1	0.9	9.8
Singapore [16]	Hospital	2012	481	47.9	14.3	7.9	2.5	27.4
Thailand [17]	Hospital	2014		37	31	22	10	

SVD, small vessel disease; LAA, large artery atherosclerosis; CE, cardioembolism.

Epidemiology of ICH

ICH is a leading cause of mortality and disability in many parts of Asia. The largest proportion of ICH incident cases and deaths occur in low- and middle-income countries in Central and Southeast Asia with a two-fold greater proportion of ICH in low-income countries compared with high-income countries [3]. A large population-based cross-sectional survey on cerebrovascular disease conducted in China revealed that the prevalence rate of cerebral haemorrhage (age ≥20 years) was 279.8/100,000 in men and 225.4/100,000 in women, the incidence rate 87.2/100,000 person-years in men and 77.1/100,000 person-years in women, the mortality rate 85.1/100,000 person-years in men and 69.6/100,000 person-years in women, respectively [21].

Interestingly, in parts of Asia such as China and Korea, there is a trend of decreasing ICH rates in recent years. In China, despite an ongoing demographic shift with an ageing population, the incidence rate of ICH has reduced from 96 cases to 62 cases per 100,000 individuals, along with a declining trend of mortality rate from 120.69 cases to 76.0 cases per 100,000 individuals, a decrease of 37.0% [21, 22]. A Korean study from the database of the Korean Health Insurance Review Agency during the period from 1995 to 2003 reported the incidence rate of cerebral haemorrhage in people aged 35–74 years. The age-standardized incidence of IS in the population 35–74 years of age increased annually by 7.18%, whereas haemorrhagic stroke decreased annually by 1.82%. Cerebral haemorrhage has decreased from 123/100,000 person-years to 106/100,000 person-years [23].

The frequency of cerebral haemorrhage as a proportion of all stroke subtypes in China accounted for approximately 24% of all stroke cases [22] while studies in India showed a range between 20 and 32%. The percentages were lower in Japan at 18% and equal in Korea at 24%. Broadly, these percentages differ in many countries in Asia with a range of 17–24% in Japan, Korea, Malaysia, Singapore, Indonesia, Iran, and Sri Lanka while the percentages were higher in India, Pakistan, Philippines, Vietnam, and Mongolia, which range from 20% to 47% [1, 22–27]. The frequency of cerebral haemorrhage in many Asian countries were higher than in Western countries. Overall, the single incidence rate of ICH is highest in Asia compared to other continents [28].

The leading risk factor for ICH in Asia is hypertension. According to data from a prospective cohort study of chronic diseases in China published in 2016, the prevalence of hypertension increased with age (from 12.6% at the age of 35 to 39 to 58.4% at the age of 70 to 74). In terms of gender differences, at a younger age, the prevalence of hypertension in men was higher than that in women (35–39 years old, 17.9% in men and 8.8% in women) while elderly women have a higher prevalence rate of hypertension compared to men (70–74 years old, 60.2% for women and 56.2% for men) [29, 30]. While hypertension was noted to be the main risk factor for IS and ICH, the attributable risk factor for ICH was higher for hypertension compared to IS, illustrated by the China Kadoorie Biobank Study [31].

Therapeutic Approaches for ICH in Asia

In China, common interventional procedures for patients with ICH were the evacuation of ICH (9.3%) and burr-hole drainage of ventricle/burr-hole decompression of skull (4.1%) as reported by the China Hospital Quality Monitoring System [32]. In other parts of Asia, minimally invasive techniques have been widely used [33, 34] and this technique appears promising with recent improvements [4, 35, 36]. A recent clinical trial conducted predominantly in Asia improved the outcome of patients with spontaneous ICH using a combined bundle of interventions including early blood pressure control and protocols for hyperglycaemia, fever, and rapid reversal of anticoagulation [5].

Treatment Approaches and Infrastructure for Hyperacute Stroke Services in Asia

The use of intravenous thrombolysis (IVT) and mechanical thrombectomies (MTs) in acute stroke patients varied greatly within Asia. Earlier studies showed greater use in East Asia compared to other Asian regions [37]. In Asia, most countries adopted the dosage of 0.9 mg/kg while in Japan, Pakistan, Vietnam, and in some hospitals in the Philippines and India 0.6 mg/kg was the standard dose [38].

In addition, TNK has been established as an alternative to rt-PA. The most recent evidence from Asia was reported from a multicentre, prospective, randomized, non-inferiority trial of tenecteplase versus alteplase in acute ischaemic cerebrovascular events (TRACE-2 study) conducted in 53 centres in China. Tenecteplase at a dose of 0.25 mg/kg was non-inferior to alteplase in IS patients eligible for standard IVT without concomitant thrombectomy [39].

Limitations in resources, lack of stroke awareness, pre-hospital delays, low number of neurointerventionists, high out-of-pocket expenses for alteplase and MT, as well as the lack of organized systems of care for acute stroke were the reasons why many other Asian countries have limited use of reperfusion therapies [40, 41]. The recent COVID-19 pandemic affected many healthcare systems worldwide. A decrease in the rate of utilization of reperfusion therapies occurred in many other Asian countries as resources were depleted or diverted [42, 43]. Future capacity building of stroke services in Asia will require contingencies for pandemic and other emergency situations.

The access for patients in Asia to acute stroke care (i.e., admission to acute stroke unit (ASU), availability of IVT and MT) is limited. While these therapies are determinants for the outcome of acute IS, a large disparity exists in the provision of these services in the region. The wide discrepancy in the allocation of stroke care resources was driven by socioeconomic development (gross domestic product per capita income in a country) and the geographic location (urban vs. rural residence within a country).

An international survey in 2016 across Asia showed that there were more than 600 ASUs with more than 10,000 beds in the surveyed regions. The number of ASU increased significantly between 1999 and 2012 with more than half of the units in China and Thailand [39]. In contrast, a recent paper reported that India has 400–500 ASUs for a population of 1.4 billion while Nepal has 2 ASUs [39, 44].

The Asian Stroke Advisory Panel also explored 4 indicators of acute stroke care in 12 Asian countries in a survey. These 4 indicators were (1) number of practicing stroke neurologists in the country; (2) availability of imaging facilities; (3) incidence of IVT; and (4) the admission to ASU [39]. Although MT was not a specific parameter surveyed at that time, these indicators were pre-requisites for successful provision of this therapy [39].

Survey of stroke care resources in various countries can be obtained from the published literature. However, these surveys may have been done in different time points, which makes direct comparisons difficult. For instance, China reported that there were 100,000 neurologists in 2015, giving an approximate ratio of 1 neurologist per 13,000 with the estimated population at that time point. In contrast, Pakistan, Malaysia, and Philippines have ratios of 1 neurologist to 2 million people in Pakistan, 1 neurologist to 235,000 in Malaysia, and 1 neurologist to 218,000 in Philippines. In high-income countries, the proportion of neurologists per unit population was high, ranging from one neurologist per 15,000 in Japan to one per 85,000 in Singapore. The situation is worsened by the concentration of neurologists in urban areas and capital cities. Accordingly, the ratio of neurologists per unit population in rural areas is much lower [38, 44, 45].

In comparison with data from 1999, a 2–3-fold increase in the number of neurologists in all countries was observed, indicating the growing number of neurology training facilities in the region. Stroke imaging facilities, CT and MRI scanners were available in all 12 countries. China and Japan have more than 10,000 CT scanners and more than 6,000 MRI scanners [38].

Socioeconomic status is the main driver of disparity between high-income and middle-to-low-income countries in provision of acute stroke care. In a recent survey conducted by the World Stroke Organization/World Health Organization/Lancet Neurology Commission on Stroke in 84 countries across World Health Organization regions and economic strata, ASUs were present in 91% of high-income countries in contrast to 18% of low-income countries ($p < 0.001$). Acute stroke treatments (as a composite score of 24/7 neurologist assessment, CT scanner, IVT and MT availability) were present in 60% of high-income countries compared to 26% of low-income countries ($p = 0.009$). Among these indicators, the estimated MT performed for eligible LVO patients was very low in Central, South, and Southeast Asia [46]. Overall, global MT capacity survey reported by the Society of Vascular and Interventional Neurology (SVIN) in 2020 showed that MT rate was estimated at 4% in China, 3.7% in Thailand, 0.7% in India, 0.1% in Philippines, 0.07% in Pakistan, and 0.03% in Bangladesh. These figures are unlikely to improve substantially without organizational and financial solutions [47].

Advances in Endovascular Treatment

In Asia, it has been reported that high-income countries were significantly more productive than lower-income countries in acute stroke reperfusion research [48, 49]. Several large core thrombectomy studies were done exclusively in Asia, proving that in patients with large ISs, endovascular thrombectomy improved functional outcome compared to medical care alone [50, 51]. Recent studies showed significantly better outcomes in posterior circulation large vessel occlusion. These recent studies from Asia were conducted entirely in China. BAOCHE (Basilar Artery Occlusion Chinese Endovascular Trial) [52] and ATTENTION trial [53] proved that endovascular treatment in addition to medical therapy was superior to medical treatment alone in selected moderate to severe cases of basilar artery occlusion.

Asian sites have also successfully participated in numerous studies comparing direct thrombectomy with or without IVT in ISs with large vessel occlusion. Three randomized trials of non-inferiority design from Asia (the DIRECT-MT [54] and DEVT [55] from China and SKIP [56] from Japan) showed similar 90-day functional outcome between stroke patients undergoing MT with or without adjunctive IVT in large vessel occlusion. However, two further studies from Asia-Oceania and Europe [57, 58] did not show non-inferiority of direct MT over bridging. In a recent meta-analysis, non-inferiority of direct thrombectomy versus IVT and direct thrombectomy was not established [59]. An acceptable therapeutic approach will be to continue the current practice until further evidence emerges [60].

Successful trials in the research arena have defined the frontiers of acute reperfusion therapy. In reality, there are many obstacles to the access of IVT and MT for the treatment of LVO strokes in many parts of Asia as described earlier. Patient awareness, health literacy, adherence and compliance to stroke prevention, government policy, the insurance reimbursement system, and stroke advocacy by professional bodies are additional factors affecting prompt access [61]. Due to the diversity within Asia, understanding the stroke ecosystem in each country, engagement of the stakeholders, and widespread use of telemedicine can narrow the gap between urban and rural regions in the same country.

In the global setting, digital subtraction angiography (DSA), MT, and alteplase have been listed as the "priority clinical intervention for stroke" in the latest WHO list of essential drug therapy and priority medical devices for management of vascular diseases [62, 63]. Furthermore, Mission Thrombectomy 2020+ (MT2020+), a worldwide non-profit campaign and multi-stakeholder alliance initiated by the Society of Vascular and Interventional Neurology (SVIN), has created awareness and strived to improve access to emergency MT for LVO strokes globally [47].

Spectrum of Cerebrovascular Diseases in Asia

Intracranial arterial stenosis (ICAS) is classified into atherosclerotic ICAS and non-atherosclerotic ICAS. As described earlier, atherosclerotic ICAS is one of the most common causes of stroke particularly in Asia [64] while non-atherosclerotic ICAS caused by MMD, arterial dissection, vasculitis, and vasospasm are less common [65–69]. Risk factors for atherosclerotic ICAS include systemic vascular risk factors such as hypertension, diabetes mellitus, dyslipidaemia, and cigarette smoking [64]. ICAS is more common than extracranial arterial stenosis caused by atherosclerosis in Asian populations compared to Caucasian populations [70].

MMD is an uncommon vascular disease of unknown aetiology leading to bilateral progressive stenoses of arteries in the circle of Willis. This rare condition affects children and young adults globally but is relatively more common in Asia, particularly East Asia [66–68].

In Asia, arterial dissections are present in the posterior circulation and in intracranial locations [69]. In contrast, arterial dissections occur predominantly in the anterior circulation and in extracranial cervical locations in Western countries and within Caucasian populations [71]. In a large case series in Japan, lateral medullary infarction, subarachnoid haemorrhage and cerebellar haemorrhage have been reported from intracranial arterial dissections [7]. The reasons behind these variable findings between ethnic groups in the literature have not been explained [7, 69, 71].

Other causes of stroke in Asia are related to the prevalent infectious diseases in the region such as tuberculosis, other bacterial diseases, and fungal infections [72]. For instance, central nervous system infections from these infectious agents have led to ISs. The pathophysiological mechanisms include direct effect of the pathogen, chronic inflammation, infectious triggers, endovascular thrombosis, and vasospasm.

Other uncommon conditions affecting large arteries and smaller arteries include Takayasu arteritis [73] and primary angiitis of the central nervous system [74]. Vasospasm can be triggered by subarachnoid haemorrhage, drug abuse, eclampsia, migraine, and reversible cerebral vasoconstriction syndrome [75].

Atherosclerotic Intracranial Arterial Stenosis

Atherosclerotic ICAS is one of the most common causes of stroke worldwide. This condition is associated with a high risk of recurrent stroke. There are three mechanisms leading to IS in ICAS: hypoperfusion, artery-to-artery embolism, and branch atheromatous disease. Combinations of these ischaemic mechanisms can also occur [64].

Imaging modalities to diagnose ICAS include transcranial Doppler, magnetic resonance angiography (MRA), high resolution MRI as shown in Figure 1, CT angiography and conventional DSA [64, 76]. Transcranial Doppler and MRA are useful screening tests but unreliable for precise evaluation of the degree of stenosis. CTA is more accurate than MRA for the diagnosis of ICAS. Combined MRA with the addition of CTA have been studied and compared to DSA. MRA with CTA improved sensitivity from 92% to 100% and specificity from 91% to 99%. The final predictive value was 93% [76]. Conventional angiography is the gold standard, but as an invasive technique, it is now indicated as part of interventional procedures.

Advances in vessel wall imaging with high-resolution MRI have improved the diagnostic accuracy of intracranial stenosis. This can be accomplished at a field strength of 3 Tesla, which examined the details of vessel wall and atherosclerotic plaques. Important features of intracranial atherosclerosis on vessel wall imaging for intracranial atherosclerosis include eccentric appearance of vessel wall with or without contrast enhancement [77–79]. In addition, the stenosis grade for HR MRI is in good agreement with DSA [80].

Current therapeutic strategies are based on previous clinical trials of Warfarin-Aspirin in Symptomatic Intracranial Disease (WASID) [81] and Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) [82]. American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend short-term dual antiplatelet therapy (DAPT) plus aggressive risk factor management in patients with severe ICAS in the vascular territory of IS or TIA [83]. The same guidelines stated that patients with severe ICAS in the vascular territory of IS or TIA should not receive angioplasty and stenting as a first-line therapy for preventing recurrence [83].

In Asia, cilostazol has been studied and widely used. One early study was TOSS (Trial of Cilostazol in Symptomatic Intracranial Stenosis), which recruited 135 Korean patients with acute symptomatic ICAS. The progression of ICAS was fewer in DAPT with aspirin and cilostazol than in aspirin alone with no stroke recurrence in either group during the observation period of 6 months [84, 85].

In the Cilostazol-Aspirin Therapy against Recurrent Stroke with Intracranial Artery Stenosis (CATHARSIS), involving 165 Japanese patients with symptomatic ICAS of at least 50%, there was no change in the progression of ICAS as primary endpoint. As a secondary endpoint, the composite of all vascular events and silent brain infarctions were significantly less in DAPT with aspirin and cilostazol than in aspirin alone during a 2-year observation period [86].

The Cilostazol Stroke Prevention Study for antiplatelet combination (CPSP.com) trial compared DAPT using cilostazol and single antiplatelet therapy (SAPT) with aspirin or clopidogrel in high-risk patients with IS including patients with ICAS and showed that DAPT with cilostazol had a lower risk of IS recurrence and a similar risk of severe or life-threatening bleeding compared to SAPT [87]. In a subgroup analysis, this combination of DAPT was also superior to SAPT for the prevention of recurrent stroke and vascular events without increasing bleeding risk among ICAS patients after stroke [88].

Despite use of antiplatelet therapy, risk of recurrent IS remained high. Evidence was reported from a subgroup

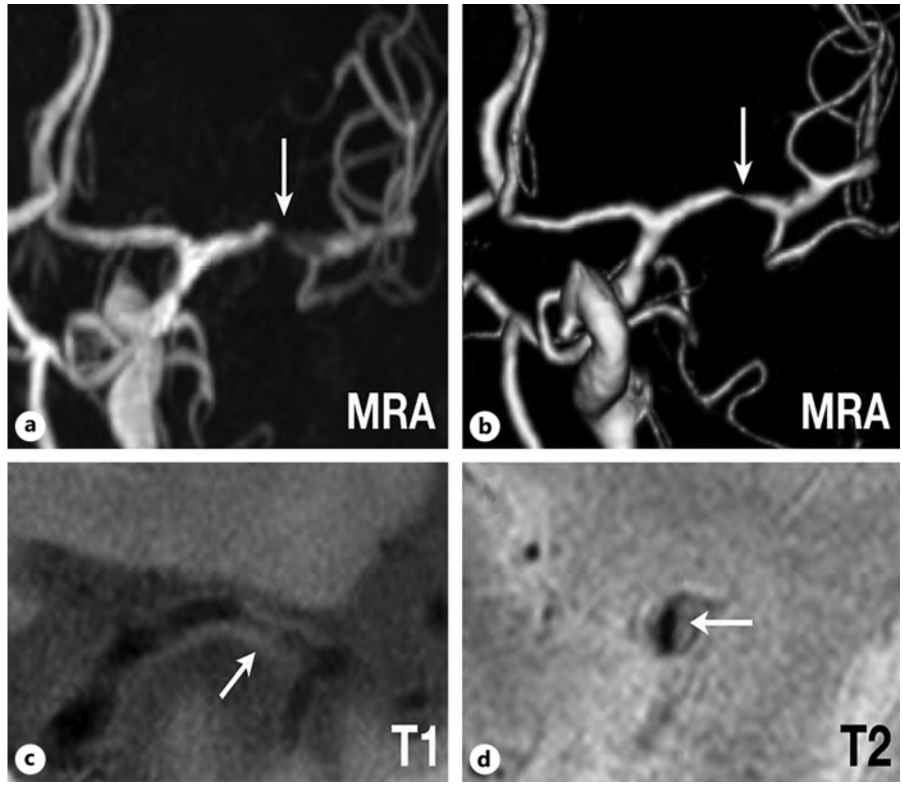

Fig. 1. Radiological findings of a 76-year-old male with atherosclerotic stenosis of the horizontal portion of the left middle cerebral artery (MCA). MRA (**a**, **b**) clearly demonstrates severe stenosis of the horizontal portion of the left MCA (arrows). High-resolution MRI shows eccentric plaque in the horizontal portion of the left MCA. **c** T1-weighted image, coronal view. **d** T2-weighted image, sagittal view.

analysis of ICAS in the CHANCE trial where the incidence of recurrent stroke was higher in patients with ICAS than in those without ICAS. However, no significant differences in stroke recurrence was detected between clopidogrel plus aspirin and aspirin alone [89]. In a population-based cohort study by the Oxford Vascular Study, risk of recurrent IS was higher in patients with symptomatic ICAS than in those without ICAS despite adherence to the current guidelines including DAPT with aspirin and clopidogrel [90].

Moyamoya Disease

MMD is a progressive vascular disorder in which arteries of the circle of Willis become stenosed or obstructed bilaterally, reducing the blood flow to the brain. Tiny blood vessels develop at the base of the brain in an attempt to supply blood to the brain. The word “moyamoya” means “puff of smoke” in Japanese, a term describing the appearance of net-like tiny blood vessels. MMD is especially common in Japan and Korea and less common elsewhere in Asia. In populations of Korea and Japan, there is also a stronger female predominance. MMD may cause headache, seizure, TIA, IS, aneurysm, or intracerebral bleeding. IS occurs in children while haemorrhagic stroke is more common in adults. In children, progressive cerebral ischaemia in MMD leads to cognitive decline and developmental delays [66, 91]. Moyamoya-like vasculopathy can develop in association with various systemic diseases and conditions, which is termed moyamoya syndrome. Ring finger protein 213 (RNF213) was identified as a susceptibility gene for Asian patients with MMD [67, 92]. Overall, there is an increased Asian-specific high prevalence of RNF213 pR4810K variant [93, 94]. It is well known that this gene variant is closely related to progressive ICAS [95]. A synergistic relationship exists between RNF213 and additional environmental as well as genetic risk factors. This gene is promising in improving the understanding of disease pathogenesis and future treatment targets for both ICAS and MMD in Asia [95, 96].

Numerous imaging techniques have continued to refine the neuroradiological features of MMD. Conventional imaging with cerebral angiography of MMD shows stenosis and occlusion of arteries of the circle of Willis with moyamoya vasculature representing collateral circulation. Flow void sign on MRI suggests moyamoya vasculature on MRI in bilateral basal ganglia [97].

As in intracranial atherosclerosis, new modalities of MR angiography can identify MMD accurately. In the diagnosis of adult MMD patients, it is often difficult to distinguish ICAS from MMD or atherosclerosis based on luminal diameter of the affected arteries. Promising neuroradiological techniques include 3-dimensional constructive interference in steady state. One study quantified the outer diameter of the terminal portion of internal carotid artery (C1) and the horizontal portion of middle and anterior cerebral artery (M1 and A1, respectively) in 64 adult patients with MMD. The outer diameter of involved arteries decreased in MMD but not in atherosclerotic stenosis as shown in Figure 2 [98].

In addition, the outer diameter of the affected arteries was found to decrease along with the disease progression and continue to shrink progressively over the next 3–12 months in MMD. Typical changes include inward remodelling, smaller outer diameters, concentric occlusive lesions, and homogeneous signal intensity. In contrast, intracranial atherosclerosis is associated with outward remodelling, normal outer diameters, eccentric occlusive lesions, and heterogeneous signal intensity [78, 97].

There is no known treatment proven to halt the progression of MMD. Surgical revascularization is an effective treatment to resolve persistent cerebral ischaemia with a reduction in ischaemia-related events such as headache, TIA, and IS. The Japan Adult Moyamoya (JAM) Trial has proven that direct or combined bypass surgery can significantly reduce the incidence of rebleeding in adult patients with ICH [99, 100].

Surgical procedures can be classified into three categories: indirect bypass, direct bypass, and combined bypass. Indirect bypass procedures are based on the fact that gradual angiogenesis occurs between the vascularized donor tissues attached to the surface of the brain and provides collateral blood flow to the operated hemispheres several months after surgery. Such spontaneous angiogenesis is a specific phenomenon for MMD [67]. Indirect bypass procedures established collateral channels in almost all paediatric patients. In contrast, indirect bypass was successful in only 50–80% of adult patients with MMD. As several months are needed to establish adequate collateral circulation, there is a higher risk of ischaemic complications during the perioperative and post-operative period [67, 101].

Direct bypass procedures such as superficial temporal artery to middle cerebral artery anastomosis rapidly improve cerebral haemodynamics after surgery. There is reduction of the risk of perioperative ischaemic stroke or TIA. Direct bypass procedure can be complicated by post-operative hyperperfusion with serious neurological outcomes [66].

Direct and indirect bypass procedures can be performed simultaneously. In centres of excellence, combined bypass procedures such as superficial temporal artery to middle cerebral artery anastomosis and encephalo-myo-duro-arterio-pericranial synangiosis can widely supply collaterals to the MCA and ACA territories as shown in Figures 3 and 4 with good long-term outcomes over 5–20 years while reducing the risk of cerebrovascular events to 0.1% per patient-year after this combination treatment [101, 102].

Radiation Vasculopathy

Radiation vasculopathies include heterogenous vascular pathologies from radiation-induced damage. The differing vascular pathologies are influenced by the underlying malignancies, radiation protocols, and patient comorbidities. Radiation field, dose, fractionation, and patient factors contribute to the rate and extent of development of atherosclerosis. Radiation therapy is widely used for nasopharyngeal carcinoma (NPC). Consequently, radiation-induced carotid artery atherosclerosis (RICA) is common after head and neck irradiation. It is the most common radiation vasculopathy in many parts of Asia due to the high prevalence of NPC [103, 104]. Radiotherapy is utilized due to limitations of curative surgery in the complex nasopharyngeal area [105, 106]. A meta-analysis of 19 published studies reported a prevalence of RICA of 25% (>50% carotid artery stenosis), 12% (>70% stenosis), and 4% (carotid artery occlusion) over an average follow-up duration of 2–13 years after head and neck irradiation [105]. NPC patients with radiation therapy had increased risk of carotid stenosis with a relative risk of 4.17 ($p < 0.00001$) compared to non-irradiated patients. In addition, an increased incidence of carotid artery stenosis measuring 50% or more was observed with a relative risk of 8.72 ($p < 0.00001$) [106].

Pathophysiological mechanisms for radiation-induced vasculopathy include DNA damage, oxidative stress, apoptosis, and activation of inflammatory cascade leading to endothelial damage, vascular remodelling, and accelerated atherosclerosis [107]. These structural changes are also associated with an increased risk of vascular events [107, 108].

Radiation atherosclerosis is more extensive than standard atherosclerosis in the irradiated neck [106, 109–111]. Irradiated plaques were also more likely to be ulcerated with mobile components. They can be calcified and less likely to contain lipid [111, 112]. Irradiated plaques were more likely to progress with 15.4% rate of progression from <50% carotid stenosis to ≥50% annually compared to 4.8% in non-irradiated plaques [113].

In view of the progressive nature of RICA, routine screening for carotid artery stenosis has been advocated.

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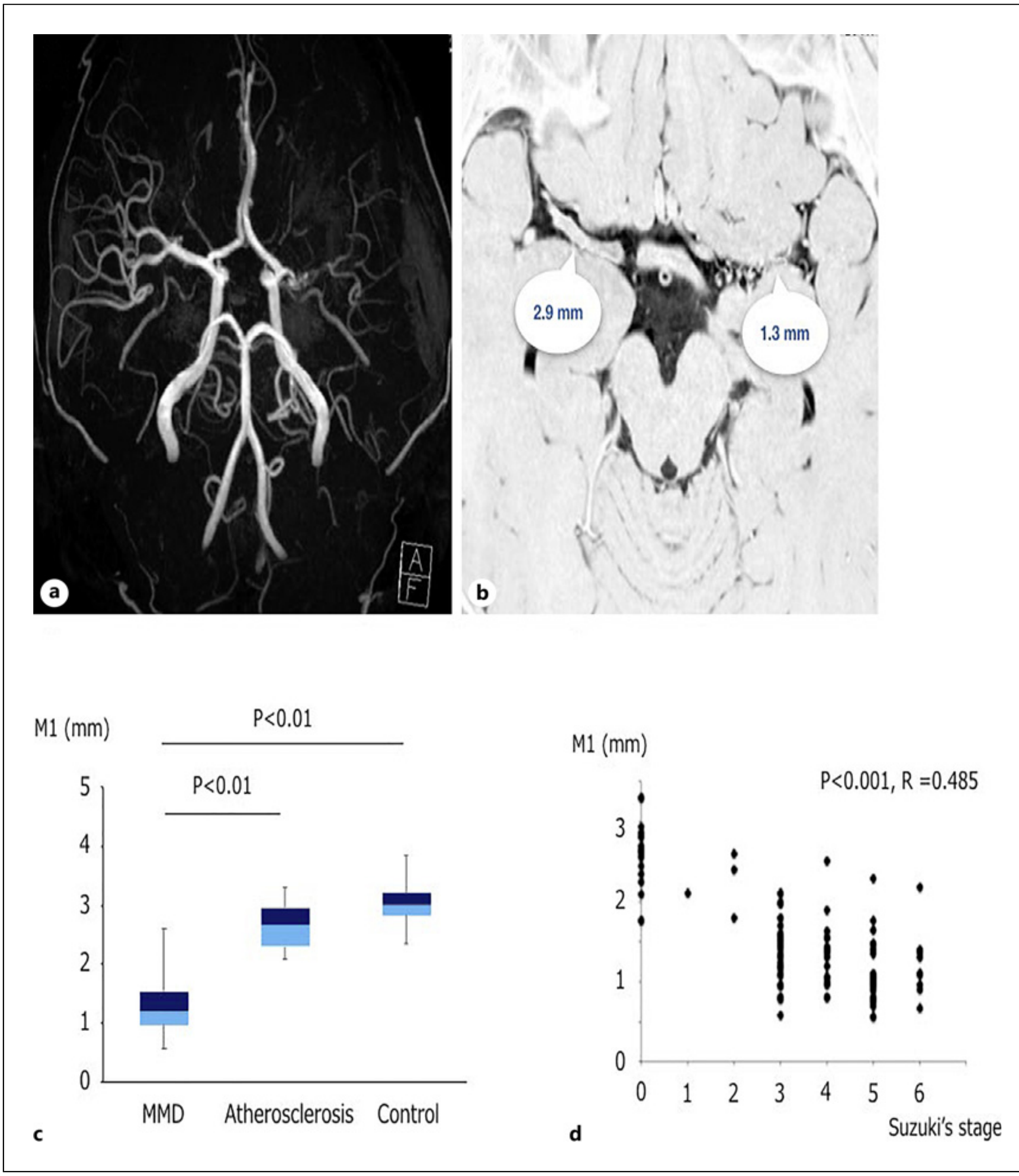

Fig. 2. MRA (**a**) and 3-dimensional constructive interference in steady state (3D-CISS) (**b**) of a 44-year-old female with unilateral moyamoya disease (MMD). Note that the outer diameter of the horizontal portion of the middle cerebral artery (M1) is markedly reduced on the left side (1.3 mm), compared with the right side (2.9 mm). **c** A column graph demonstrates the outer diameter of the M1 portion is smaller in patients with MMD than in those with atherosclerosis and controls. **d** A scatter graph shows that the arterial shrinkage in the M1 portion well correlates with the Suzuki's disease stage in MMD.

A proposed surveillance strategy utilizes interval screening with carotid ultrasound 1 year after radiation therapy [105, 106]. Observational studies on stenosis rates of irradiated carotid arteries of ≥50% at 2, 3, and 4 years were 4%, 11%, and 14%, respectively. Significant (>70%) carotid stenosis was more likely after an interval of >5 years post-radiation therapy. This supports early carotid Doppler screening within the first few years [109, 114, 115]. In addition, the presence of traditional cardiovascular risk factors have been implicated in the

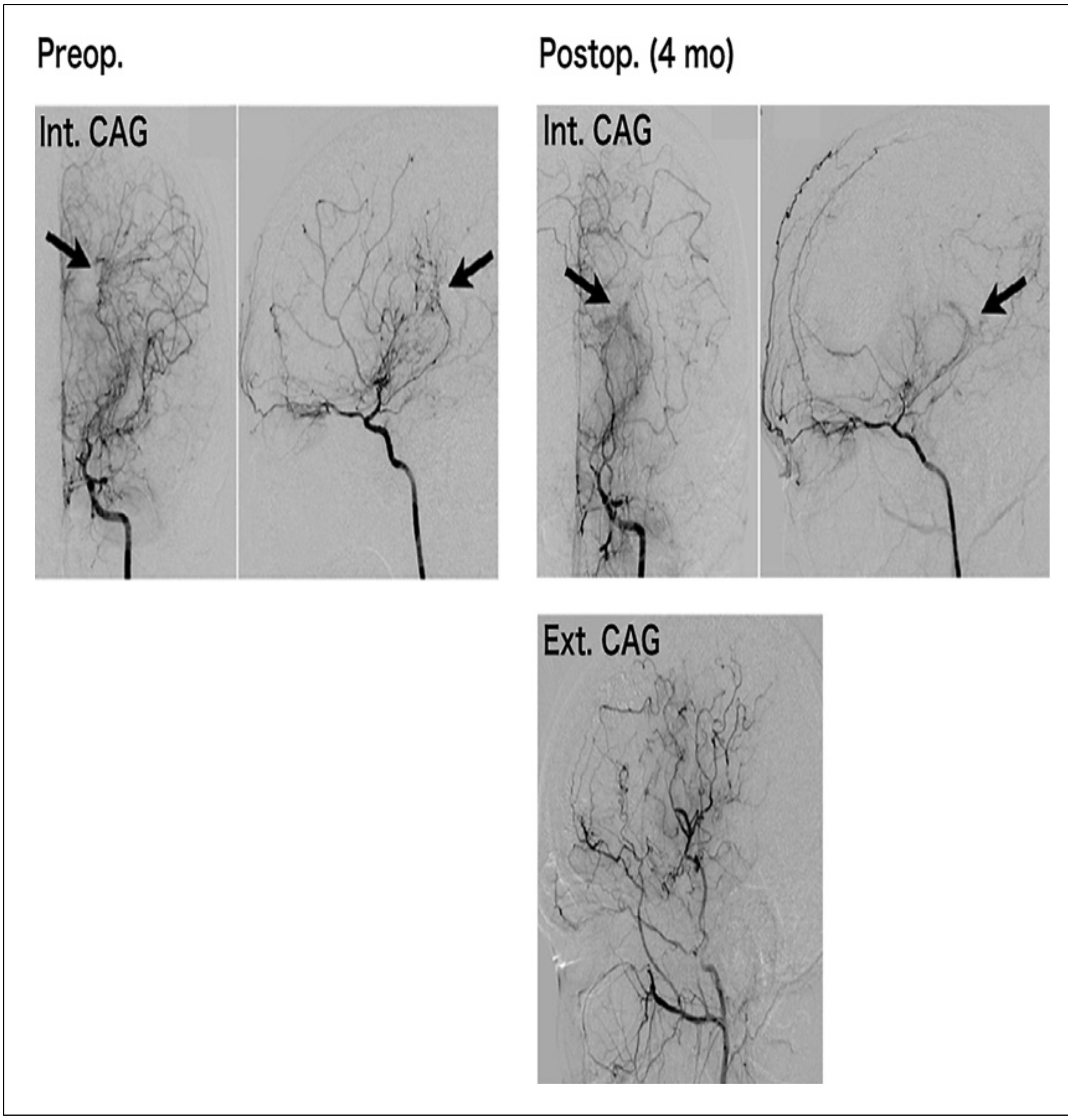

Fig. 3. Pre- and post-operative findings on cerebral angiography in an 8-year-old boy with MMD. Before surgery, left internal carotid angiography demonstrates a marked stenosis of the carotid fork associated with the development of moyamoya vessels. Note that the moyamoya vessels originating from the anterior choroidal artery are markedly dilated (arrow). On follow-up, left internal carotid angiography was performed 4 months later after STA-MCA anastomosis combined with EDMAPS (see the text); the extent and diameter of the moyamoya vessels markedly diminished (arrow). On external carotid angiography, the surgical collaterals through direct and indirect bypass are well developed and widely supply the blood flow of the operated hemisphere.

progression of RICA. Early identification and initiation of best medical therapy may retard this progression [105, 106, 113].

In carotid revascularization, carotid artery angioplasty and stenting (CAS) is preferred because of local tissue alterations post-irradiation, longer arterial lesions, and higher complications associated with carotid endartectomy (CEA). Recognized post-operative wound complications occurred in 14% while cranial nerve injuries occurred in 28% with CEA, compared to 5% and 9% in CAS patients, respectively [116]. In contrast, other studies reported that with careful selection, CEA is as safe and effective as CAS [112, 117]. Studies from Southeast Asian centres have reported favourable experiences with CAS [118, 119]. Intra-stent stenosis is a common complication of CAS with

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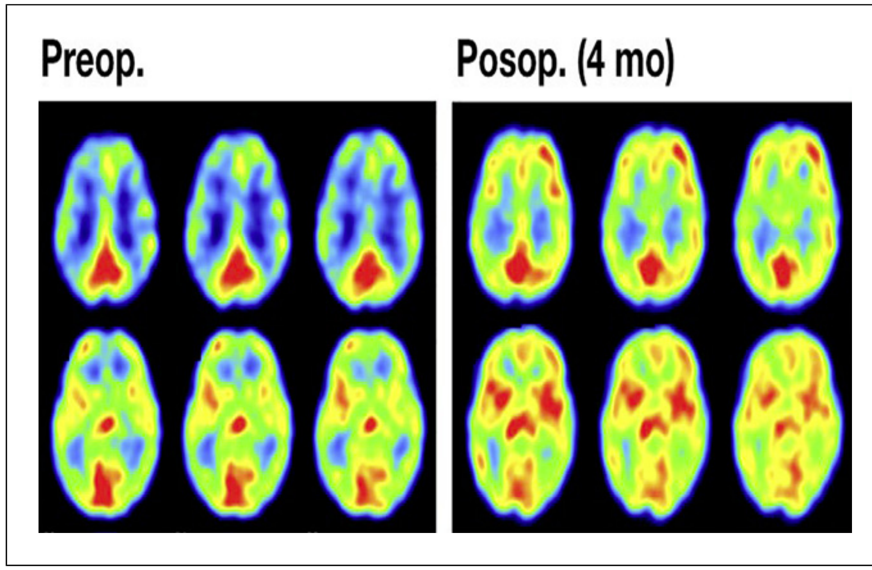

Fig. 4. Pre- and post-operative findings on 123 I-IMP single photon emission computer tomography (SPECT) in an 8-year-old boy with MMD. Before surgery, cerebral blood flow is markedly reduced in the territory of the internal carotid artery on both sides. Note the disappearance of hyperfrontality. Bilateral STA-MCA anastomosis combined with EDMAPS markedly improved cerebral haemodynamics in the bilateral hemispheres.

studies reporting >50% stent re-stenosis ranging from 15.8% to 50% within 36 months [117, 120].

Radiation-induced endothelial damage may lead to vascular remodelling. Radiation vasculopathy of the cerebral vessels can also present as moyamoya syndrome or focal stenoses in the paediatric population. Large and small vessel disease, telangiectasia, microangiopathy, and aneurysms have been described with cranial irradiation [118, 119, 121–124].

Observational studies have reported that the risk of developing intracranial aneurysm was highest in patients with NPC who received radiotherapy with a 2.57 hazard ratio compared to patients without radiotherapy. In addition, a significant risk factor for the development of aneurysm was hypertension [121]. Approximately 50% of these aneurysms present with intracerebral and subarachnoid bleeding with 25% mortality [122]. Another study identified 46 patients with 69 intracranial aneurysms observed over a 35-year period from 1978 [125]. Saccular aneurysms were the most common at 83% while pseudoaneurysms were less common at 9%. The median time to identification ranged from 6 to 20 years, depending on the type of radiation therapy used. Stenoses were reported within the shortest time with radiation used in stereotactic surgery and the longest with brachytherapy [126]. However, the optimal strategy for radiation-induced aneurysms is unclear.

The definitive treatment for radiation vasculopathy is uncertain and is likely to correlate closely with patient comorbidities, type of cancers treated, type of radiation therapies, time after radiation, and the frequency of screening. There are insufficient data to guide optimal management due to the lack of clinical trials. Recognized therapeutic strategies include the use of antithrombotics or revascularization for the different types of radiation vasculopathies. Further research is needed to define the best care for radiation vasculopathy.

Infections and Stroke in Asia

Systemic and central nervous system infections are uncommon causes of stroke in Asia. However, it is essential to recognize and identify them in order to provide proper diagnosis and treatment. Direct invasion of the nervous system and intracranial vessels from adjacent infection can cause ischaemic and haemorrhagic stroke. Tuberculous meningitis-related IS occurs mostly at the basal ganglia secondary to basal arachnoiditis around the arteries of the circle of Willis. Tuberculous meningitis should be suspected in patients with stroke occurring 10–14 days after a meningitic syndrome and fever [127]. Rarely, IS occurs as a complication of bacterial meningitis [128, 129].

Rhinocerebral mucormycosis and aspergillosis are angioinvasive fungal infection, which can locally invade intracranial vessels leading to ischaemic and haemorrhagic stroke in immunocompromised patients [130]. Stroke due to meningovascular syphilis can occur at the average of 7 years after the primary infection [131]. Gnathostomiasis is a parasitic infestation that can migrate to the skin and penetrate into the central nervous system causing subarachnoid haemorrhage and migratory ICH [132]. These unusual conditions have been reported in Asia.

Systemic infection can also result in stroke. Infective endocarditis can lead to embolic stroke and subsequent mycotic aneurysm. Fever, systemic symptoms, anaemia, and peripheral signs of embolic phenomena are the clues to diagnosis [133]. When suspected, echocardiogram and blood cultures should be performed. Some systemic infection can cause haematologic derangement, leading to thrombotic or haemorrhagic complications. Thrombocytopenia in patients with dengue haemorrhagic fever can result in intracranial haemorrhage [134]. Patients with HIV infection are at higher risk of stroke due to several mechanisms including direct viral invasion of the cerebral vascular wall, hypercoagulable state due to protein C and protein S deficiency, marantic endocarditis, and stroke related to opportunistic infection as well as antiviral treatment-induced atherosclerosis [135].

Stroke is a well-recognized complication of SARS-CoV-2 infection in Asia and worldwide especially in patients with pre-existing diseases and cardiovascular risk factors. Large vessel occlusion and multiple territorial stroke in patients with severe COVID-19 disease were reported [136, 137]. Severe COVID-19 is related to activation of proinflammatory cytokines and prothrombotic state, causing venous and arterial thromboembolism including reported cases of CVT. Antiphospholipid antibodies were also found in some patients [137].

Patients with suspected infection-related stroke warrant appropriate investigations and management. Haemostatic abnormalities should be promptly corrected in patients with haemorrhagic stroke or infection-related prothrombotic state. Antimicrobial treatment for infection is essential in most cases. Antiplatelet and antithrombotic treatment should be carefully assessed. In some circumstances, treatment of inflammation including immune mediated reaction need to be considered. For example, steroid treatment is needed in patients with stroke-related tuberculous basal arachnoiditis. Surgical treatment may be required to remove the infected tissue in patients with sinus-related fungal infection or complicated infective endocarditis despite adequate antibiotic treatment.

Cerebral Venous Thrombosis

CVT is an uncommon but important cause of stroke in Asia particularly in younger patients. The annual incidence rate of CVT in the Ludhiana urban population-based stroke registry from India was 1.31/100,000 [138]. The mean age of CVT patients in the Asian study of CVT was 31 years. The common risk factors identified in the Asian CVT cohort were anaemia, use of oral contraceptive pills, pregnancy and postpartum period, as well as central nervous system infections [139]. More recently, additional risk factors, which are well recognized, include COVID-19 infection and COVID vaccine-induced immune thrombotic thrombocytopenia [140].

In a study from South India among pregnancy-associated CVT, 71% of women had single prothrombotic factor while 34% had multiple prothrombotic factors. Methylene tetrahydro-folate reductase heterozygosity, factor V Leiden heterozygous mutation, hyperhomocysteinemia, and elevated factor VIII levels were the important risk factors. In this cohort, the regional practice of restricting water during peri- and post-partum period was common [141]. In a large CVT study of 970 cases from India, an increase in incidence of CVT was reported during the summer months particularly for patients below 40 years of age [142]. The common clinical presentations reported were seizures, focal deficits, headache, and features of raised intracranial pressure. The diagnosis was established by CT scan (plain/contrast), MRI/MRV, or DSA.

The management of CVT requires targeting multiple pathophysiological processes. In order to facilitate venous return, nursing with head end elevation, avoiding neck flexion, tight elastic mask bands, internal jugular vein catheters, and high positive end expiratory pressure during ventilation should be performed. Systemic anticoagulation has proven benefit [143] even with haemorrhagic venous infarcts [144]. Studies support low-molecular weight heparin over unfractionated heparin [145, 146]. In post-acute phase, oral anticoagulants (vitamin K antagonists) can be initiated.

Direct oral anticoagulants were found to be as effective as vitamin K antagonists [147]. The optimal duration of oral anticoagulation is unclear and subjected to a clinical trial [148]. Lifelong treatment is recommended with underlying severe thrombophilia.

Systemic thrombolytic agents are not recommended [149]. Many case series have shown the safety and benefits of endovascular treatment with the objective of recanalizing the obstructed venous system in selected patients. The strategies used were endovascular thrombolysis and MT [150, 151]. However, no benefit was observed in a recent randomized controlled trial comparing thrombectomy with anticoagulation. The study was underpowered while the thrombectomy arm received heterogeneous treatment [152].

The treatment of raised intracranial pressures from vasogenic or cytotoxic edema is effective with hyperosmolar therapy. Carbonic anhydrase inhibitors can reduce CSF production [153] while therapeutic serial lumbar punctures in selected cases may also be useful [154]. Steroids are not recommended except in the context of CVT from underlying autoimmune diseases [155]. Antiepileptic drugs are recommended in cases with seizures and large supratentorial cortical lesions [156, 157]. However, the evidence for the use of prophylactic AEDs in those without seizures at presentation is uncertain [158]. Retrospective case series have shown benefits of decompressive surgery with large supratentorial venous infarcts with impending herniation as a life-saving measure [159]. Studies including a prospective study on decompressive surgery in CVT have also shown benefit [159, 160]. Overall, there is a wide spectrum of presentations and outcomes in cerebral venous thrombosis. Indicators of poor prognosis include status epilepticus, deep venous system involvement, the presence of midline shift, and diffuse cerebral oedema [160].

Conclusion

This review covered the spectrum of cerebrovascular disease across Asia while highlighting unique epidemiological features of stroke in Asia. These conditions were described along with the most recent developments in acute stroke therapy within the existing systems of stroke care in Asia. More research, awareness, and funding for the described cerebrovascular diseases in Asia will be required in the future to optimize the care of affected patients. Access to funding and capacity building for hyperacute stroke care will also be required for many of the less developed countries across Asia.

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Statement of Ethics

No approval from Ethics Committees is required in this paper, which is based on publicly available publications.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.S.T. conceptualized the outline of the entire paper, revised and re-organized most of the manuscript for length, and updated content and clarity. All authors contributed by writing their respective sections and have read and approved the final version of this manuscript. J.D.P. and S.A. co-wrote the section on CVT, K.T. and T.W.H.L. co-wrote the original sections on acute stroke care infrastructure and research in Asia. N.V. and L.P.L. co-wrote the epidemiology of ischaemic stroke and intracerebral haemorrhage. S.U. and S.K. co-wrote the section related to moyamoya disease and provided the figures and illustrations on MMD. N.C.W. wrote the section on infection and stroke. H.M.C. wrote the segment on radiation vasculopathy.

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