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HYPERTENSION AND STROKE SUBTYPES: A CAUSATIVE ROLE OR SIMPLE ASSOCIATION?

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INTRODUCTION

Stroke is the second leading cause of death worldwide following CV disease, associated with poor prognosis, a high rate of recurrence, increased mortality and rising costs to the health care system. The complex and multifactorial pathogenesis of stroke determines clinical course and outcomes. Among numerous cardiovascular (CV) risk factors, hypertension is a critical determinant of the increased risk for developing ischemic stroke (IS) and haemorrhagic stroke (HS). More than 12 million strokes are attributable to elevated blood pressure (BP) with an increased risk of acute stroke in prehypertension and younger population. [1] The differences in the incidence of stroke dependent on race, ethnicity, gender, age, socioeconomic status. African Americans have approximately twofold increased risk for developing stroke when compared to Caucasians. More recently, genetic components, gene mutations associated with folate metabolism, chronic stress, short-term use of nonsteroidal anti-inflammatory drugs in hypertensives, job strain and long working hours have been demonstrated to substantially increase the risk of stroke. Women have greater incidence of primary or recurrent strokes and associated death with the underlying mechanisms not entirely understood. The gender specific stroke-related risk factors including pregnancy, pre-eclampsia, gestational hypertension, hormonal contraception, menopause, hormone replacement therapy, metabolic syndrome, obesity, atrial fibrillation (AF), migraine with aura and smoking may play critical role in this scenario. [2]
Overall, 77% of all strokes are first off events and the risk of having a transient ischaemic attack (TIA) or recurrent stroke within the first year is nearly one in four. [1] Despite concerns raised over cerebral perfusion, blood flow and BP levels after stroke, ample evidence demonstrates that a reduction in BP is the most important intervention for primary and secondary stroke prevention with the gradual reduction in stroke mortality largely attributable to improved hypertension control. [3,4]

ISCHEMIC STROKE

IS accounts for 87% of all strokes with the remaining 13% attributable to haemorrhagic stroke (HS). More than 150 known causes of stroke have been identified to date with numerous classification systems (i.e. Harvard Cooperative Stroke Registry, Oxford Community Stroke Project, TOAST, SSS-TOAST, ASCO classification) defining the subtypes of acute IS. While there are some strengths and limitations regarding the various categorizations, the narrow time window for therapeutic action in acute IS critically requires the appropriate identification of stroke subtype and underlying cause. Clinical outcomes after stroke, stroke recurrence rates and approaches for secondary prevention are strongly dependent on stroke subtype. Recent advances in brain imaging have contributed to the precise identification of stroke subtype likely resulting in improved clinical outcomes. This indicates that consistent categorization of patients according to stroke type and associated mechanisms is crucial in clinical trials in acute IS. Likewise, the use of detailed stroke subtyping system consistently applied among clinicians and researches is relevant in meta-analysis and clinical trials assessing the effectiveness of therapies and outcomes.

Large artery atherosclerotic disease stroke subtype

Large artery atherosclerosis (LAA) appears to be an important target for primary prevention of stroke. Intracranial atherosclerosis underlying stroke development is higly prevalent in China and Thailand with similar findings in Japan, Singapore and Korea. [5] More recently, the Rotterdam study has assessed the Caucasian population-attributable risk (PAR) for having a stroke secondary to calcification in each of the four vessel beds (intracranial carotid arteries, extracranial carotid arteries, aortic arch, coronary arteries). [6] Using the formula which provides a measure between 0% and 100% (based on the relative risk and the presence of calcification), intracranial carotid artery atherosclerosis accounted for 75% of all strokes, calcification of aortic arch contributed to 45% of strokes and extracranial carotid artery calcification accounted for 25% of acute cerebrovascular events [6] indicating that intracranial LAA is the most common vascular lesion and major risk factor for stroke. Given that the sum of PARs exceeds 100%, a possible interaction between risk factors cannot be ruled out. Hemodynamically significant stenosis or occlusion of a major brain artery or branch cortical artery confirmed with duplex imaging or arteriography is important in the classification of stroke secondary to LAA. Patients with hypertension, diabetes, metabolic syndrome, dyslipidemia and aortic or coronary plaque are at high risk of developing LAA stroke with a strong likelihood of atherosclerotic vascular disease in other peripheral arteries accompanying concomitant intracranial atherosclerosis. [7,8] Intracranial large artery disease (ICLAD) plays a leading causative role in IS and is particularly prevalent among Asians [9] with hypertension being a strong independent risk factor for ICLAD but not extracranial carotid disease. However, traditional risk factors such as age, hyperlipidemia, diabetes and ischemic heart disease are associated with both atherosclerotic sites, intracranial and extracranial. [10]

Cardio-aortic embolism subtype

Available evidence indicates cardioembolic stroke (CES) comprises 14-30% of all ischemic strokes [11] and 20% of all cerebral infarctions in North American and European populations. [12] Numerous cardio-aortic sources have been shown as critical contributors to high primary risk of cerebral embolism with the most clinically relevant including AF, recent myocardial infarction, mechanical prosthetic valve, dilated myocardiopathy, and mitral rheumatic stenosis. [11] While the prevalence of sources with low or uncertain primary risk of stroke (i.e. patent foramen ovale, atrial septal aneurysm, complex atheroma in an aorta etc.) are not uncommon in the general population though their direct relation to the CES mechanisms have been less apparent. [13] The presence for example of large atheromas in the ascending aorta and the aortic arch has been linked to an increased risk of CES in patients over the age of 60 and in patients after cardiopulmonary bypass or cardiac catheterization. However, it remains unclear whether atheroma thickens is a direct mechanism underlying stroke or a marker for other conditions (i. e. generalized atherosclerosis or intracranial atherosclerosis). This could partly explain the findings of the Rotterdam study in which intracranial atherosclerosis was a major risk factor for stroke. [6] Moreover, the presence of calcification within the atheroma has been found to decrease the risk of stroke when compared to noncalcified lesions (ulcerations or mobile components in the atheroma). [13] Several clinical characteristics are indicative of CES including sudden onset of neurological deficit, reduced level of consciousness, 'spectacular shrinking deficit syndrome' (rapid onset of a major hemispheric stroke syndrome followed by abrupt recovery associated with migration of an embolus), Wernicke's aphasia or global aphasia in the absence of hemiparesis. [11] The short and long-term prognosis of patients with CES differs from other stroke subtypes with the high rate of recurrent stroke and in-patient mortality at one month. [11] Patients with IS and AF commonly have worsened neurological recovery, clinical prognosis and high risk for recurrent stroke when compared to patients with normal sinus rhythm. [14] Patients with excessive alcohol intake, hypertension, valvular heart disease, nausea, vomiting and previous ischemic stroke confer augmented risk of early recurrent embolization. [11]

Small artery occlusion (Cerebral small vessel disease, CSVD) subtype

Lacunar infarcts (LI) accounts for ~25% of all ischemic strokes. The presence of clinical features and radiological signs of typical small infarcts confirm small artery occlusion stroke type. Patients with LI, subcortical or brain stem infarcts with a diameter ranging from 0.2 to 15-20 mm follow into this category. [15] Autopsy studies have recognized two types of LI with possibly different vascular pathology; lipohyalinosis and microatheroma. [16] Patients with LI may present with a single lacune which is likely to have atherosclerotic risk factors or multiple lacunes with strong link to hypertension. [17] The strong association between lipohyalinosis and hypertension has been documented in several studies. [18] Neurological outcome, recurrent stroke and increased mortality risk in patients with lacunar stroke and at least one asymptopmatic lacunar lesion have been shown to be worse when compared to LI lacking these lesions. [18] The contribution of hypertension and diabetes as independent determinants of multiple LI is well recognized. [19] Resonance imaging studies have found that reduced estimated glomerular filtration rate (eGFR) has been related to CSVD (i.e. reduced white matter volume, increased white matter lesions, small brain volume) independently of CV risk factors. [20] Patients with lower eGFR appear to have more LI. The close association between retinopathy and CSVD that causes white matter lesions and lacunes have been observed in hypertensives and normotensives. [21] However, not all patients with LI have presented with a history of elevated BP or glucose levels indicating that pathophysiology of CSVD is more complex than anticipated. Atherosclerotic carotid plaque or cardiac embolic source has been shown to be contributing mechanisms underlying LI with or without presence of hypertension and diabetes. There is evidence linking genetic predisposition, parental history of stroke, gene polymorphism and inflammatory markers to small vascular infarction. [22]
The term 'hypertensive cerebral small vessel stroke' is broad and includes LI and hypertensive primary (non-traumatic) deep intracerebral haemorrhage (ICH). Similarly to LI, hypertension is not always an underlying cause of primary ICH. Other contributors such as high monocyte count beyond traditional risk factors (i.e. current smoking status and hyperlipidemia) has been related to the development of clinical LI in patients with acute hypertensive small vessel disease stroke but not deep ICH. [23] The presence of LI and white matter lesions on MRI substantially increased the risk of vascular and nonvascular death, and future IS in patients with symptomatic atherosclerotic disease. [24] Whether silent clinically asymptomatic

infarcts have prognostic significance merits further research.

Other determined causes

This category includes the conditions that bore close temporal and spatial association with acute cerebral infarction including nonatherosclerotic vasculopaties (i. e. fibromuscular dysplasia (FMD), arteritis, migraine), haematological disorders (abnormalities of thrombosis and hemostasis), drug-induced stroke, moyamoya disease, meningitis, sickle cell disease, arterial dissection, Sneddon syndrome and others. FMD is a vascular disease associated with secondary hypertension. While it most commonly affects renal arteries, if present in carotid or vertebral arteries plays a causative role in TIA, aneurysm, artery dissection, ischemic stroke and subarachnoid haemorrhage (SAH). [25]

Undetermined causes

The substantial proportion of patients suffered an IS have a defined background aetiology. However, despite a comprehensive diagnosis based on the exclusion of the other potential causes, up to 40% of TIAs or strokes with varying proportions dependent on the patient population are of uncertain or undetermined causes, commonly known as cryptogenic TIA or cryptogenic stroke (CS), cryptogenic embolism, incomplete evaluation and unclassified categories. The distribution of CS in numerous studies in North American and European populations has averaged ~25% and most cryptogenic strokes are of thromboembolic origin. [12] Unravelling the cause of the stroke remains particularly challenging in younger patients (<50-55 years of age) in whom ~40-60% of strokes are of cryptogenic origin. [26] Recently, data from 15 European stroke centres has demonstrated that 39.6% of patients aged 15-49 years had undetermined aetiology of cerebrovascular events [27] with increasing prevalence of CS <35 years of age. [28] Patients with CS stroke display a greater risk for recurrent stroke suggesting that additional occlusive artery lesions is likely to be a contributing mechanisms of stroke recurrence after CS. [29] However, patients with CS displayed less hypertension, diabetes, peripheral vascular disease, hypercholesterolemia or history of smoking. Additionally, CS bore no excess risk of asymptomatic carotid disease or acute coronary events, no further risk of minor risk of echocardiographic abnormalities, paroxysmal AF prior to stroke occurrence or new AF after stroke or presumed cardioembolic events. [30] The rate of recurrent stroke in patients with CS may differ between studies as a result of using dissimilar diagnosis criteria and/or classification. Nevertheless, given the global burden attributable to CS, a need to further research on potential causes, treatments and secondary prevention is warranted.

HAEMORRHAGIC STROKE

The appropriate identification of stroke-related symptoms and differentiation between IS and HS subtype at onset of disease is critical in providing prompt diagnosis and immediate treatment. While the incidence of HS is 7-10 times lower when compared to ischaemic subtypes, severity and associated increased mortality is greater in HS than IS. [31] Survival following HS is determined by the area of brain bleeding and related tissue damage. SAH and ICH are the two major types of HS. Although underlying pathophysiology, treatment and prognosis depend on the type of haemorrhage, if not diagnosed and treated promptly SAH and ICH result in a loss of cognitive function and subsequent death.

Subarachnoid haemorrhage

The rupture of intracranial (brain) aneurysm (saccular type aneurysm) is considered the leading cause of SAH accounting for 85% of cases [32] with the remaining spontaneous causes including non-aneurysmal perimensencephalic haemorrhage and rare abnormalities (i.e. arterial dissection, cerebral arteriovenous malformation, dural arteriovenous fistula, vascular lesion around the spinal cord, septic aneurysm, pituitary apoplexy, cocaine abuse).

Among all attributable risk factors, cigarette smoking, hypertension, excessive alcohol consumption and a first degree relative with history of the condition are critical in triggering SAH. [33] Autosomal dominant polycystic kidney disease, positive family history of intracranial aneurysm of SAH, brain tumour, pituitary adenoma or atherosclerosis female gender and subjects >50 years of age have been shown to be associated with a greater risk of the incidence of unruptured intracranial aneurysm.

Intracerebral haemorrhage

ICH accounts for ~10-20% of all strokes. [34] The incidence of ICH in Asians is nearly twofold when compared to other ethnic groups. [35] This observation indicates that Asians are prone to developing not only IS underlying LAA but also ICH stroke. In general, women appear to have a lower incidence of ICH than men. [35] The pathophysiology of ICH is complex involving numerous risk factors and multiple underlying mechanisms with hypertension playing a causative role in triggering primary ICH. [36] History of hypertension has been found in ~90% of patients demonstrating ICH. [37] The risk of developing ICH is nearly fourfold higher in hypertensive subjects than normotensives and increases with BP levels. [38] Markedly elevated BP on hospital admission and inadequate BP control have adversely contributed to prognosis in hypertensive ICH. [37] In fact, a substantial proportion of haemorrhages are likely to be associated with noncompliance to antihypertensive medication in addition to reflex mechanisms secondary to the increase in intracranial pressure and/or the mass-effects produced by the size of the hematoma. While the clinical symptoms associated with ICH depend on size and location, the most common clinical features of intracerebral bleeding in hypertensive patients include hemiparesis/hemiplegia, aphasia with headache, vomiting and seizures. In addition to hypertension, aging has been demonstrated as the leading unmodifiable risk factor for developing ICH with a nearly tenfold increase in octogenarians when compared to middle-aged subjects. [35] Further risk factors including cigarette smoking and alcohol intake have been directly related to an increased risk of ICH in the INTER-STROKE study. [36]

It is noteworthy to mention that cerebral microbleeds (CMBs) are indicative of CSVD caused by leakage of blood vessels resulting in accumulation of blood in the brain tissue. CMBs can occur in the heathy population, mostly in the elderly and have ~30% prevalence in IS and ~60% contribution to non-traumatic ICH. [39] CMBs are commonly found in patients with hypertension without a history of cerebrovascular disease and have been independently related to ambulatory BP levels. [39,40] Microbleeds confers the risk of recurrent ICH. [41] Whether CMBs should be considered a marker of hypertension-induced organ damage merits further investigation.

Haemorrhagic transformation of ischemic stroke

Haemorrhage transformation (HT) is haemorrhage secondary to IS and affects ~9% of patients with prognosis depending of the type of HT. HT is associated with a complication following trombolysis (i.e. tissue plasminogen activator, rtPA) in acute IS or natural evolution of a cerebral infarction. [42] CT imaging divides HT into two major types including haemorrhagic infarction (HI) and parenchymal hematoma (PH). Although the mechanisms underlying HT are not completely understood, several factors and predictors including massive cerebral infarction, AF, cerebral embolisms, hypergycemia and thrombolytic therapy have been found to predict HT, mainly PH. [43]

FUTURE AND PERSPECTIVES

Prevention of stroke remains a challenging clinical problem. Given the complexity of heterogeneous and incompletely understood pathophysiology underlying stroke, a need to continue with further clinical research to gain a better understanding of risk factors, clinical markers and outcomes associated with specific stroke subtype clearly exists. Although lowering BP and improving adherence to medication can substantially reduce the risk of stroke, available evidence indicates that not all stroke subtypes is caused by established hypertension. The use of consistent classification of stroke types using clinical and radiological approaches in determining the associated mechanisms, effectiveness of therapies and prognosis across large global trials is justified.

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