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Cerebrovascular Disease and Hypertension

Navdeep Singh Sidhu and Sumandeep Kaur

Abstract

Systemic hypertension is a major public health problem, nearly affecting one-third of the global adult population. It is the leading modifiable risk factor for coronary heart disease (CHD), cerebrovascular disease, renal dysfunction, peripheral arterial disease (PAD), heart failure and atrial fibrillation. Human brain is one of the most important target organs for hypertension related end-organ damage. Two major categories of hypertension related cerebral diseases include stroke and dementia, which are associated with considerable morbidity and mortality. Large body of clinical evidence has shown that adequate control of elevated blood pressures (BPs) could be a very effective tool in reducing the incidence and prevalence of cerebrovascular diseases. In the following sections, we discuss the role of hypertension in the causation of cerebrovascular disease along with the preventive and therapeutic strategies for the same.

Keywords: cerebrovascular disease, stroke, dementia, blood pressure, hypertension, intracranial hemorrhage, management, brain, cerebral, ischemic

1. Introduction

Systemic hypertension is one of the most common and devastating disorders affecting the human race. It is a major cause of premature death worldwide and is the risk factor with greatest impact on the global burden of disease. It is the leading modifiable risk factor for cardiovascular disease and all-cause mortality [1, 2].

Worldwide, an estimated 1.38 billion individuals (31.1% of the adult population) have hypertension, defined as systolic blood pressure (BP) $\geq$ 140 mm Hg and/or diastolic BP $\geq$ 90 mm Hg, and/or current use of antihypertensive medication. The age-standardized prevalence of hypertension is marginally higher in men (31.9%) than in women (30.1%) and is lower in high-income countries (HICs), as compared to low and middle-income countries (LMICs) (28.5% vs. 31.5%) [3]. According to global estimates in 2010, only 45.6% of individuals with hypertension were aware of the disease, only 36.9% were receiving treatment and only 13.8% had achieved adequate BP control (defined as systolic BP < 140 mm Hg and diastolic BP < 90 mm Hg). Also, the proportion of hypertension awareness and treatment was nearly twice and the proportion of hypertension control was four times in HICs as compared to LMICs. In the last 2 decades, HICs have shown substantial increases in the proportions of hypertension awareness, treatment and control. However, during the same period, awareness and treatment have increased only modestly in LMICs and the proportion of hypertensive patients having adequately controlled BP has decreased slightly [3].

The global prevalence of hypertension is increasing steadily as a result of aging of the population and increase in lifestyle risk factors like unhealthy diets (high sodium, low potassium intake, high intake of saturated and trans-fats and low intake of fruits and vegetables), physical inactivity, increased consumption of alcohol and tobacco, and being overweight or obese. However, the changes in the prevalence of hypertension have not been uniform worldwide. In the last two decades, a modest decline has been noted in hypertension prevalence in HICs, whereas LMICs have experienced significant increases. These trends can impose a greater burden of hypertension and related cardiovascular disorders on the fragile health-care systems of LMICs, many of which are also facing a substantial burden of infectious diseases [4].

Hypertension is often called a "silent killer", as most hypertensives are unaware of the problem due to lack of warning symptoms or signs. Hypertension can cause sub-clinical target organ damage for years, before any symptoms or signs develop. It is the leading modifiable risk factor implicated in the causation of coronary heart disease (CHD), cerebrovascular disease, renal dysfunction, peripheral arterial disease (PAD), heart failure and atrial fibrillation. The brain is a major target for hypertension related end-organ damage and hypertension is a prominent risk factor for two major categories of brain diseases: stroke and dementia. In the following sections, we discuss the role of hypertension in causation of these diseases, along with prevention and treatment strategies.

2. Hypertension and brain

Human brain, in general, is highly vulnerable to the harmful effects of elevated BP and it represents the classic target organ of hypertension-induced damage. Arterial hypertension, besides being responsible for its well-known effect in causing clinical stroke, is also associated with the development of asymptomatic, subclinical brain damage, such as cerebral small vessel disease with resultant cognitive impairment, memory loss and dementia. Also, sudden and marked elevations of blood pressure can lead to the development of hypertensive encephalopathy, characterized by severe headache, seizures and other neurological symptoms like cerebral edema.

2.1 Hypertension and stroke

2.1.1 Hypertension as a risk factor for stroke

Globally, stroke ranks second among the causes of mortality and third among the causes of disability. In recent decades a trend towards reduction in the incidence, prevalence and mortality of stroke has been noted, but the overall disease burden continues to rise in terms of total number of patients affected [5].

Stroke is usually categorized into ischemic and hemorrhagic forms. Ischemic stroke has further subtypes including large vessel occlusive disease, lacunar infarctions due to small vessel disease, cerebral embolism including cardioembolic stroke, non-atherogenic stroke and cryptogenic stroke. Various subtypes of hemorrhagic stroke include intra-parenchymal hemorrhage, subarachnoid hemorrhage and intraventricular hemorrhage.

Hypertension is the most prevalent risk factor for stroke and has been reported in nearly two-thirds of stroke patients [6]. In LMICs, the reported prevalence of risk factors among patients with stroke is lower, however the in-hospital mortality rates have been higher, probably related to delays in presentation, differences in healthcare system responses and acute management of stroke [7].

There is robust evidence from observational and interventional studies, implicating hypertension as a strong risk factor for all types of strokes. The Framingham heart study in 1970 showed a significant association between the risk of stroke and blood pressure ≥ 160/95 mm Hg at all ages and in both sexes [8]. Persons with a normal BP (<120/80 mm Hg) had been reported approximately half the lifetime risk of stroke compared to those with high BP (≥140/90 mm Hg) [9].

Large epidemiological studies have consistently shown the relationship between the level of BP and risk of stroke to be consistent, continuous, and independent of other risk factors. Older epidemiological studies gave more importance to the diastolic BP as a determinant of stroke risk, and consistently showed a higher risk of stroke with increasing levels of diastolic BP [10, 11]. MacMahon et al., in their meta-analysis of nine observational studies conducted between 1958 and 1990, showed that as the level of BP decreased so did the risk of stroke. A decrease in diastolic BP of 5, 7.5, and 10 mm Hg was associated with a lowering of stroke risk by 34, 46, and 56%, respectively [11]. Similarly, The Eastern Stroke and Coronary Heart Disease Collaborative Research project, showed that for every 5 mm Hg fall in the diastolic BP resulted in nearly 50% reduction in the risk of ischemic (odds ratio (OR) 0.61; 95% confidence interval 0.57–0.66) and hemorrhagic stroke (odds ratio 0.54, 95% confidence interval 0.50–0.58) [12]. Systolic BP attracted greater attention in 1990s after the results from many epidemiological studies suggested that it could have more robust association with stroke as compared to diastolic BP. Systolic BP also showed a stronger correlation with 12 year stroke mortality than the diastolic BP in Framingham heart study [13]. Similarly, the prospective population-based Copenhagen city heart study demonstrated systolic BP to be a better predictor of stroke than the diastolic BP [14]. The Asia Pacific Cohort Studies Collaboration (APCSC), an extension of the Eastern Stroke and Coronary Heart Disease Collaborative project, which analyzed 37 cohort studies of 425,325 patients in the Asia Pacific region, demonstrated a continuous, log-linear association between systolic BP and risk of stroke down to the levels of 115 mm Hg of systolic BP. In the age groups of <60, 60–69, and >70 years, a 10 mm Hg lower systolic BP was associated with 54%, 36% and 25% lower risk of stroke respectively [15]. In a meta-analysis of 61 prospective studies by the Prospective Study Collaboration (PSC), it was demonstrated that there was more than a twofold decrease in stroke mortality with each 20 mm Hg of decrease in systolic BP for patients aged 40–69 years; and throughout middle and old age, usual BP is directly and strongly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115 mm Hg of systolic BP and 75 mm Hg of diastolic BP [16].

Age is an important cofactor in the relationship between hypertension and stroke. The direct relation between elevated BP and stroke risk is weaker in older aged populations than in middle-aged individuals. The APCSC observed a lower percentage reduction in stroke risk with similar reduction in systolic BP with increasing age [15]. A similar trend was observed in the PSC study [16]. Although there is a less robust association between hypertension and stroke risk in older populations, lowering BP in this population is still beneficial owing to the higher incidence of stroke and higher morbidity/mortality rates in this population [17].

Racial and ethnic disparities in the relationship between elevated BP and stroke have been reported from several observational studies from the United States. The Baltimore-Washington Cooperative Young Stroke Study, demonstrated a positive relationship between hypertension and the risk of ischemic stroke in whites and blacks for both sexes. In this study, age-adjusted odds ratios and 95% confidence interval for ischemic stroke with a history of hypertension in white males, white females, black males, and black females were 1.6 (0.7–3.2), 2.5 (1.1–5.9), 3.8 (1.8–7.9), and 4.2 (2.4–7.5), respectively [18]. Similarly, the Northern Manhattan Stroke

Study showed higher odds ratios for hypertension and ischemic stroke in blacks as compared to whites and hispanics (OR 2.0 vs. 1.8, 1.2 respectively) [19]. A similar increase in systolic BP is associated with a nearly three times higher risk of stroke risk in blacks as compared to whites [20].

2.1.2 Hypertension related stroke and its pathophysiological mechanisms

Although arterial hypertension is a major risk factor for both stroke and myocardial infarction, stroke is much more closely related to elevated levels of BP per se. It has been suggested that a sustained reduction in systolic blood pressure of 10 mm Hg would reduce stroke risk by 56%, but reduce the risk of myocardial infarction by only 37% [11]. This difference is largely attributed to the possibility that elevated levels of blood pressure are directly responsible for strokes occurring due to small vessel disease, but is only indirectly related to the development of atherosclerotic changes. Atherosclerosis in the arterial tree is usually focal and is usually seen at the branching points of the arteries or where arteries take a bend. It is likely that the effects of hypertension on atherosclerosis are not per se due to pressure energy, but are more likely related to the transmission of kinetic energy to the arterial wall at sites of flow disturbance, thus leading to the formation of atherosclerotic plaques at the areas of low shear stress [21].

Strokes due to small vessel disease, in contrast, are directly caused by elevated blood pressure. For this reason, these tend to occur in a particular distribution at the base of the brain, where short, straight arteries with limited branches result in direct transmission of high blood pressure directly from the large arteries to the smaller resistance vessels, with resultant damage to the walls of the arterioles. This results in the pathological changes of hyaline degeneration and fibrinoid necrosis, with consequent lacunar infarctions where the arterioles occlude and hypertensive intracerebral hemorrhages where they rupture. These pathophysiological changes account for the fact that true lacunar infarctions and intracerebral hemorrhages are particularly distributed in the areas of basal ganglia, internal capsule, thalamus, cerebellum, and brainstem [22].

Hypertension can indirectly contribute to the development of stroke as it is an important etiological factor for atrial fibrillation and for acute myocardial infarction and left ventricular clot formation; with attendant risk of cardioembolic stroke.

There are many theories related to the pathophysiological mechanisms of hypertension related brain dysfunction. Central to these theories are the mechanisms related to impaired cerebrovascular auto-regulation in hypertension and the chronic maladaptive changes in the structure of the cerebral vasculature in hypertensive patients.

Cerebrovascular autoregulation is the process by which cerebral vasculature regulates intracranial blood flow, so that a steady perfusion is maintained to meet the metabolic needs of the brain tissue across a range of systemic blood pressures. This control is achieved by the ability of the cerebral arterioles to compensate for a decrease in cerebral perfusion pressure by vasodilatation, and also, to protect the brain against increased perfusion pressure by vasoconstriction, thus keeping the cerebral blood flow constant. This complex process is regulated by interplay between sympathetic nervous system, brain carbon dioxide and other metabolites, and neurovascular coupling. In normotensive individuals, this response occurs over a range of approximately 60–160 mm Hg systolic BP; but, in patients with hypertension, this range may be shifted to higher pressures [23, 24]. This upward shift in the limits of pressure autoregulation, make hypertensive patients especially susceptible to episodes of hypotension, which plays a role in the development of white matter changes. Also, elderly hypertensive patients often have impaired

cerebrovascular autoregulation which contributes to the development of stroke, cognitive dysfunction and vascular dementia. Impaired autoregulation increases the transmission of elevated pressures to cerebral capillaries resulting in increased permeability of blood brain barrier (BBB), parenchymal edema, inflammation neuronal degeneration that is commonly seen in patients with vascular cognitive dysfunction [25]. Chronic hypertension has been reported to promote arteriolar and capillary rarefaction, especially in the deep hemispherical white matter and basal ganglia [26]. This is associated with infiltration of perivascular macrophages, endothelial dysfunction, increased oxidative stress, and impaired functional hyperemia [27]. These changes promote the development of lacunar infarcts, white matter hyper-intensities, microinfarcts, and microbleeds [28].

Chronic elevation of intraluminal pressure stimulates the growth of smooth muscle cells and increases media thickness in resistance arteries, resulting in hypertrophic remodeling, thus causing an elevated vascular resistance. There may also be eutrophic remodeling, characterized by inward remodeling with rearrangement of the vessel wall components that leads to a reduction in lumen diameter and elevated vascular resistance. Hypertension may also result in narrowing of the intermediate and small vessels due to lipo-hyalinosis and micro-atherosclerosis. Also, chronically elevated BP promotes hyaline degeneration, fibrinoid degeneration and formation of microaneurysms in small vessels of the cerebral vasculature. These small vessel alterations predispose these patients to the development of ischemic and hemorrhagic complications [29].

Hypertension promotes atherosclerosis in large extracranial and intracranial arteries, which predispose to the development of atherothrombotic infarctions. The most frequent sites of atherosclerosis are common carotid artery bifurcation, origin and intra-cavernous part of internal carotid artery, first segment of middle cerebral artery, origin and distal part of vertebral artery, and middle portion of basilar artery [29]. These atherosclerotic plaques are usually progressive and lead to ischemic strokes by thrombotic occlusion of the narrowed lumen or, more often, by their acute rupture, which causes atheroembolism resulting in occlusion of distal intracranial vessels [29]. Major mechanisms of hypertension related cerebral dysfunction are summarized in **Table 1**.

2.1.3 Blood pressure management for primary and secondary stroke prevention

2.1.3.1 Hypertension control for primary stroke prevention

The relation between BP and stroke risk is direct, strong, linear, and etiologically predictive. Thus, within the usual BP ranges, including non-hypertensive ones, the higher levels of BP are associated with increased risk of stroke [16]. Non-hypertensive individuals with slight elevations of BP (prehypertension, defined as systolic BP of 120–139 mm Hg and/or diastolic BP of 80–89 mm Hg) derive benefit

Impairment of cerebral autoregulation
Increased permeability of blood brain barrier
Endothelial dysfunction, oxidative stress, impaired functional hyperemia
Small vessel changes: remodeling, increased vascular resistance, lipo-hyalinosis, micro-atherosclerosis, micro aneurysms, lacunar infarcts
Large vessel changes: atherosclerosis with atherothrombotic, atheroembolic infarctions

Table 1.
Potential mechanisms of hypertension related cerebral dysfunction.

from lifestyle changes with or without pharmacological therapies. A meta-analysis with 70,664 prehypertensive individuals from 16 trials demonstrated a robust 22% reduction in the stroke risk in individuals randomized to pharmacological therapy arm as compared to the placebo arm. In hypertensive patients, lifestyle approaches combined with adequate BP treatment and control produced a 35–40% decrease in the stroke risk [30, 31].

Practical strategies for hypertension management for primary stroke prevention, on the basis of recommendations made by the American Heart Association (AHA)/American Stroke Association (ASA) [32, 33], and European Society of Cardiology (ESC)/European Society of Hypertension (ESH) [34] include:

1. Regular screening for hypertension and management of raised BP using lifestyle modifications and pharmacological therapies are recommended.

2. According to European guidelines the target BP in those with hypertension should be <140/90 mm Hg, whereas, the recent American guidelines recommend a BP goal to lower levels of <130/80 mm Hg, even in very elderly.

3. Successful attainment of BP goal is emphasized over the administration of a particular anti-hypertensive agent.

4. Individualized BP treatment is recommended, based on particular patient characteristics and tolerance to medications.

5. Self-monitoring of BP is recommended to help in adequate BP control.

2.1.3.2 Hypertension management in acute ischemic stroke

Management of elevated BP in acute ischemic stroke (AIS) has been a matter of considerable debate. AIS is usually associated with islands of infarcted tissue with surrounding areas of potentially salvageable tissue, referred to as ischemic penumbra. Moreover, the infarcted tissue is characterized by loss of autoregulation with increased vessel permeability [35]. Hence an over aggressive approach of lowering BP can result in extension of infarction and worsening of neurological dysfunction. On the other hand, if the elevated BP is not lowered sufficiently, there is risk of excessive cerebral edema and hemorrhagic transformation of the infarcted tissue. Furthermore, as the cerebrovascular auto regulatory response is set at a higher level in chronic hypertensive patients, these individuals are at risk of impaired cerebral perfusion if BP is lowered very aggressively.

Practical strategies for management of hypertension in AIS, based on recommendations of AHA/ASA [36], and European stroke organization (ESO) [37] include:

1. In patients with AIS who are not eligible for systemic thrombolysis or mechanical thrombectomy and who have a BP > 220/120 mm Hg, guarded BP reduction (<15% systolic BP reduction over 24 h) is reasonable and is likely to be safe. No recommendations are made regarding the use of a specific anti-hypertensive agent to achieve this goal.

2. In hospitalized patients with AIS and blood pressure < 220/110 mm Hg not treated with intravenous thrombolysis or mechanical thrombectomy, there is suggestion against the routine use of blood pressure lowering agents at least in first 24 h following symptom onset, unless this is necessary for specific comorbid

conditions like acute aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy and acute renal failure.

3. In patients with AIS undergoing treatment with intravenous thrombolysis (with or without mechanical thrombectomy) it is suggested that BP is maintained below 185/110 mm Hg before bolus and below 180/105 mm Hg after bolus, and for 24 h after alteplase infusion.

4. In patients with AIS undergoing treatment with intravenous thrombolysis (with or without mechanical thrombectomy), there is suggestion against lowering systolic blood pressure to a target of 130–140 mm Hg compared to <180 mm Hg during the first 72 h following of symptom onset.

5. Initiating or continuing anti-hypertensive agents during hospitalization for AIS, if BP > 140/90 mm Hg: BP lowering is generally safe in AIS if patient is medically and neurologically stable, and there are no contraindications for BP lowering. The time window for administration of such therapies is usually 2–3 days after the symptom onset.

Drug options to treat hypertension in patients with AIS who are planned for emergency reperfusion therapy are shown in **Table 2**.

2.1.3.3 Hypertension management in acute hemorrhagic stroke

Observational studies have suggested that BP is often markedly elevated in the acute phase of hemorrhagic stroke, significantly higher than that seen after AIS [38]. High levels of BP in acute hemorrhagic stroke are often associated with hematoma expansion and poor clinical outcomes [39]. Simultaneously, there have been suggestions that high BP may be necessary to maintain adequate cerebral perfusion after intracranial hemorrhage, and that aggressively lowering it may be deleterious. These concerns are however, opposed by the evidence suggesting that adequate cerebral perfusion is maintained after acute BP reduction in patients with hemorrhagic stroke [40, 41]. However, results of the two largest randomized clinical trials (INTERACT2, ATACH-2) of intensive BP lowering early after intracranial hemorrhage have renewed this uncertainty [42, 43]. Meta-analyses of these trials and many other smaller studies have shown that early intensive BP reduction after hemorrhagic stroke is safe, but without mortality benefit or significant functional improvement [44–47]. In contrast, a recent meta-analysis of the two largest trials demonstrated a direct linear relation between the level of systolic BP

Labetalol: 10–20 mg intra-venous over 1–2 min, may be repeated once; or
Nicardipine: 5 mg/h intra-venous, dose may be up-titrated by 2.5 mg/h in every 5–15 min to a maximum of 15 mg/h; when desired BP levels is obtained, adjust the dose to maintain proper BP levels; or
Clevidipine: 1–2 mg/h intra-venous, up-titrate by doubling the dose in every 2–5 min until desired BP level is obtained; maximum dose 21 mg/h
Other agents like enalaprilat, hydralazine may also be useful
If BP is not controlled or diastolic BP > 140 mm Hg, consider intravenous nitroprusside (may increase intracranial pressure).

Table 2.
Drugs for acute management of elevated blood pressures in patients of acute ischemic stroke who are planned for emergency reperfusion therapy [36, 37].

achieved during the first 24 h of hemorrhagic stroke and the functional status. The improvements in the functional status were noted for systolic BP levels of as low as 120–130 mm Hg [48]. These studies however excluded patients with severe, large hematomas and hence caution is warranted in too aggressive lowering of BP in such patients as it might predispose to harmful consequences [49].

Practical strategies for BP control in patients with acute hemorrhagic stroke based on recent AHA/ASA [50], and ESO [37] guidelines include:

1. If initial systolic BP is >220 mm Hg, it is reasonable to administer continuous intravenous BP lowering therapy to achieve an initial reduction of about 15%. Choice of drugs is similar to that used in AIS (**Table 2**).

2. In patients with initial systolic BP of 150–220 mm Hg, American guidelines suggest a target goal of 140–150 mm Hg of systolic BP [50], however, the recent ESO guidelines [37] recommend even more aggressive lowering of systolic BP to less than 140 mm Hg (but to keep it above 110 mm Hg) to reduce hepatoma expansion.

3. Control of blood pressure variability may be helpful in improving the outcomes [51].

4. After hemorrhagic stroke, the optimal timing for initiation of antihypertensive therapies for secondary stroke prevention has not been well established. It may be reasonable to start such treatment when the patient is medically and neurologically stable. The target BP goal for secondary stroke prevention is <130/80 mm Hg [50].

2.1.3.4 Hypertension management for secondary stroke prevention

About a quarter of strokes are recurrent, the annual risk of recurrence is nearly 4% and the mortality rate after a recurrent stroke is 41% [33, 34]. A large proportion of strokes can be prevented by adequate BP control, regular physical activity, healthy dietary habits and cessation of smoking. In fact, the INTERSTROKE study demonstrated that these 5 factors—hypertension, imbalanced diet, lack of adequate physical activity, abdominal obesity and smoking—were responsible for 82% and 90% of the population attributable risk (PAR) for ischemic and hemorrhagic stroke respectively [6]. Also, the Global Burden of Disease Study suggested that nearly 90% of the global stroke burden was attributable to the modifiable risk factors [52]. A modeling study has shown that targeting multiple modifiable risk factors of stroke has additive benefits in secondary prevention of stroke. According to this study, aspirin, anti-hypertensive therapies and statins, along with dietary modification and adequate exercise, can lead to an 80% cumulative risk reduction in the incidence of recurrent vascular events [53].

Practical strategies for BP control for secondary recent AHA/ASA guidelines [54] include:

1. In hypertensive patients who suffer a stroke or transient ischemic attack (TIA), an office BP goal of <130/80 mm Hg is recommended for most patients to reduce the risk of recurrent stroke and vascular events.

2. In individuals with no history of hypertension who experience a stroke or TIA and have an average office BP of ≥130/80 mm Hg, antihypertensive drug treatment can be beneficial to decrease the risk of recurrent stroke, intracranial hemorrhage, and other vascular events.

3. A thiazide diuretic, angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) may be useful, however, other classes of BP lowering therapy can be used to achieve the target BP goals (e.g., calcium channel blocker, newer generation beta blocker).

4. Individualized drug treatments that take into account patient comorbidities, pharmacological class of the drug, and patient preferences are recommended to maximize the drug efficacy.

2.2 Hypertension and dementia

2.2.1 Hypertension as a risk factor for cognitive dysfunction and dementia

Dementia is characterized by a progressive and often irreversible decline of cognitive function which is most commonly seen in older adults. It is one of the most common neurological diseases, nearly affecting 30–40 million people worldwide. The number of people with dementia is estimated to triple by 2050, largely driven by the aging of the population, demographic shifts, and lack of disease-modifying therapies [55]. Alzheimer disease (AD) and cerebrovascular diseases are the major causes of cognitive dysfunction, accounting for nearly 80% of the cases and often have a mixture of both the pathologies [55]. Although the majority of dementias including AD are primarily considered as neuro-degenerative diseases of unknown cause, recent studies have shown that cerebrovascular disease and microscopic vascular lesions are often found in patients affected by these conditions [56].

The term vascular cognitive impairment (VCI) refers to the entire spectrum of cognitive abnormalities caused by vascular etiologies, whereas the term vascular dementia is used for cases with more profound vascular cognitive deficits which negatively affect the daily functioning of an individual [57].

Among the various vascular risk factors, systemic hypertension is a major factor contributing to cognitive impairment [57]. It has been been associated with decreased abstract reasoning, reduced mental processing speed, and, less commonly, memory deficits [58]. Although dementia due to AD and vascular dementia have classically been considered as separate entities, recent evidence indicates that the two conditions are frequently coexistent [59, 60]. In nearly 40–50% of cases with a clinical diagnosis of AD, the pathological hallmarks of AD (amyloid plaques and the neurofibrillary tangles), are associated with micro-cerebrovascular and macro-cerebrovascular lesions [61]. Moreover, ischemic lesions markedly elevate the effect of AD pathology on cognitive function [62, 63]. Also, traditional cardiovascular risk factors have been suggested to have a role in the development of AD [64], and some estimates suggest that risk factor modification, especially the treatment of hypertension, could decrease the incidence of clinically diagnosed AD by up-to 30% [65].

2.2.2 Mechanisms of hypertension related cognitive dysfunction

Hypertension-related cognitive dysfunction occurs as a result of complex interplay between functional alterations and structural changes seen in the brain parenchyma and the cerebral vasculature, many of which have been discussed previously in Section 2.1.2. Briefly, these changes include increased cerebrovascular resistance, reduced vasomotor reactivity, decreased cerebral blood flow, vascular remodeling, lacunar infarcts, white matter lesions, micro bleeds, enlarged perivascular spaces and cerebral atrophy [66]. These overlapping pathophysiological changes might account for the correlation between hypertension and stroke or vascular dementia.

This relation may also hold true for other forms of dementia; like, for example the link between chronic hypertension and the AD has been documented, as hypertension is often associated with formation of neurofibrillary tangles and senile plaques, the presence of which was seen in brains of hypertensive patients even in the absence of clinical features of dementia [67].

2.2.3 Prevention of cognitive dysfunction by antihypertensive therapy

Hypertension is a major modifiable risk factor for cognitive dysfunction, VCI and AD. Robust clinical evidence has demonstrated that antihypertensive therapies, besides preventing major cerebrovascular events [57], also reduce the incidence and/or delay the progression of cognitive dysfunction [68, 69]. The Syst-Eur randomized clinical trial showed that, on treating 1000 hypertensive individuals with anti-hypertension therapies for 5 years, 19 cases of dementia could be prevented [70]. Similarly, the PROGRESS trial observed that therapy with a perindopril (a long-acting ACE inhibitor), and indapamide (a thiazide-like diuretic), was associated with reduced risks of cognitive dysfunction and dementia on a mean follow-up of 3.9 years [71]. Also, various clinical and experimental studies have suggested that antihypertensive drugs, including ACE inhibitors, angiotensin receptor blockers (ARBs) and diuretics, might cause an improvement in the biomarkers of AD, and decrease the incidence of AD and/or delay its progression [72].

Interestingly, antihypertensive drug therapies might have class specific effects on cognitive function. Both ACE inhibitors and calcium channel blockers have been reported to delay the development of cognitive dysfunction [72]. However, results from the Canadian Study of Health and Aging suggested that hypertensive individuals aged ≥65 years who received treatment with calcium channel blockers had a more marked cognitive decline than those receiving other antihypertensive drugs at follow-up of 5 years [73]. These findings lend support to the hypothesis that the systemic and local renin-angiotensin systems may respond differently to different antihypertensive drugs [74]. Furthermore, calcium channel blockers may potentially cause an impairment of myogenic autoregulatory protective responses in the cerebral vasculature. Taking these factors into account, it might be suggested that ACE inhibitors and ARBs might be preferable to calcium channel antagonists for dementia prevention in hypertensive patients [75].

The subject of optimum BP targets for the prevention of dementia has generated considerable debate and controversy. In the SPRINT MIND trial, it was seen that in ambulatory hypertensive individuals, a more intensive BP control strategy (target systolic BP of <120 mm Hg as compared to a target of <140 mm Hg) was not associated with any significant cognitive benefits [76]. An important point to be considered here is that due to the adaptive rightward shift of the cerebrovascular autoregulatory curve in hypertension, too aggressive lowering of BP may result in cerebral hypoperfusion and consequential negative impact on the brain. These U-shaped associations between BP and cognitive function in the elderly individuals have been reported in many studies [77, 78]. These findings stress the importance of individualized blood pressure management strategies for prevention of cognitive dysfunction.

Hypertension is also a major contributor to the risk of stroke, which nearly doubles the risk of developing dementia. It is estimated that about one-third cases of dementia can be prevented by preventing the development of stroke [79]. Clinical studies have shown that prevention of stroke by using anticoagulation in atrial fibrillation and BP-lowering therapies in hypertensive patients can significantly decrease the risk of dementia [80]. Based on these results, the World Stroke Organization came out with a manifesto stressing the need for a joint strategy for prevention of stroke and dementia [79].

3. Conclusions

Hypertension is a major global public health problem and is the major cause of premature death worldwide. Human brain is highly vulnerable to the deleterious effects of elevated blood pressures. Hypertension related cerebrovascular diseases include stroke, cognitive dysfunction and dementia. Elevated blood pressure levels are strongly, directly and linearly related to the incidence and prevalence of these diseases. Adequate management of hypertension can go a long way in mitigating the global burden of these cerebrovascular diseases.

4. Final remarks

Elevated systemic blood pressures are associated with increased risk of cerebrovascular diseases including stroke and dementia. Good blood pressure control, which can be achieved easily in majority of the patients, is necessary for prevention of these cerebrovascular diseases.

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