Blood pressure and the brain: the neurology of hypertension

Dearbhla M Kelly, Peter M Rothwell

ABSTRACT
Hypertension affects more than one in four adults. The brain is an early target of hypertension-induced organ damage, and may manifest as stroke, subclinical cerebrovascular abnormalities and dementia. Hypertension-related small vessel disease can cause vascular dementia and can potentiate Alzheimer’s pathology, lowering the threshold at which signs and symptoms manifest. Many hypertensive emergencies may also have a neurological presentation, such as hypertensive encephalopathy, haemorrhagic stroke or pre-eclampsia. Here we highlight the importance of blood pressure in maintaining brain health and the brain’s role in controlling blood pressure.

INTRODUCTION
The global prevalence of hypertension is estimated to be 1.13 billion. Hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke. Given that stroke accounts for the largest share of the neurological burden of disease, hypertension is increasingly recognised as a global neurological problem. Here we explore the role of the brain in blood pressure (BP) control, the impact of hypertension on cerebral physiology and some of the clinical consequences, including cerebrovascular disease, dementia and sleep disorders.

Is hypertension a neurological disease?
The brain plays an important role in BP homeostasis (see figure 1). The cardiovascular centre in the medulla oblongata is responsible for the regulation of cardiac output. By mediating changes in heart rate, stroke volume or vascular tone via sympathetic or parasympathetic stimulation, it facilitates the short-term control of BP, whereas renal regulation is more important for long-term control. The cardiovascular centre responds to baroreceptor signals detecting stretch, and chemoreceptor signals that detect changes in oxygen/carbon dioxide concentrations.

The rostral ventrolateral medulla and upper cervical spinal cord regions play a key role in central BP control. For example, high cervical spinal cord injury is associated with a very erratic BP; dysregulated neural network dynamics in caudal presor regions have been implicated in the development of hypertension.

The brainstem control centres may also receive modulation from higher brain regions, such as the cerebral cortex, hypothalamus and limbic system. Lesion studies of patients following epilepsy surgery have given us greater insight into cortical cardiovascular control. In a study of five patients undergoing intraoperative insulin stimulation before temporal lobectomy for seizure control, stimulation of the left insular cortex tended to produce bradycardia and depressor responses, whereas stimulation of the right insular cortex resulted in tachycardia and pressor effects; this suggests a right-sided dominance for sympathetic cardiovascular effects. Because the insular cortex is located in the region of the middle cerebral arteries, it tends to be particularly susceptible to cerebrovascular disease. Right middle cerebral artery infarction may disinhibit insular function, resulting in increased sympathetic cardiovascular tone and the cardiac consequences of stroke, including sudden death.

Further supporting evidence for the role that the brain may play in causing and maintaining hypertension is that BP starts to fall 3 years before overt development of dementia and continues to decline afterwards. Subtle neurodegenerative lesions in these strategic locations of the brain that regulate BP may initiate this premorbid decline.

Pathophysiology of hypertension-induced brain injury
At ages 40–69 years, each difference of 20 mm Hg in usual systolic BP (or, equivalently 10 mm Hg in usual diastolic BP) is associated with a more
than a twofold difference in stroke mortality. Hypertension also worsens stroke outcomes as patients with pre-existing hypertension have smaller penumbras and larger infarctions compared with those with normal BP.

Cerebral blood flow regulation in a normal brain is determined by various intrinsic control mechanisms, including myogenic/stretch, and chemical, metabolic and neurogenic control. Autoregulation ensures that cerebral blood flow remains relatively constant over a wide range of BP changes (figure 2). When extremes of BP exceed the compensatory vasoconstrictive or vasodilatory capacity, autoregulation is impaired. This usually occurs if the mean arterial BP (mean arterial pressure) falls below 50 mm Hg or rises above 150 mm Hg in a normotensive person. However, this plateau phase may be shifted to higher BP values during chronic hypertension to maintain the same level of cerebral blood flow. The exact mechanisms by which hypertension affects cerebral autoregulation are not completely understood but they likely include a combination of myogenic tone alterations and inward vessel remodelling with an increase in wall-to-lumen ratio in response to tangential stress on the artery wall.

Studies using angiotensinogen knockout mice support a role for angiotensin II in cerebral artery remodelling, with a reduction in wall thickness and wall-to-lumen ratio in aged spontaneously hypertensive rats treated with ACE inhibitors. Angiotensin II and aldosterone have been linked to the production of reactive oxygen species. Reactive oxygen species are key mediators of cerebrovascular dysfunction in hypertension, as they contribute to vessel rarefaction (loss of arterioles and capillaries) and structural remodelling of cerebral blood vessels, with resultant chronic hypoperfusion of the brain. Hypertension also enhances blood-brain barrier permeability via reactive oxygen species and impairs its ability to regulate central nervous system homeostasis. The increased blood-brain barrier permeability associated with hypertension may also be attenuated by ACE inhibition.

Arterial stiffness and hypertension
Arterial stiffness relates to age, heart rate and mean arterial BP, and in hypertensive diabetic subjects, to duration of diabetes and of insulin treatment. It is not fully understood whether stiffness is a cause or consequence of hypertension. Carotid artery stiffening was increased independently of BP only in young patients with hypertension, and not in older ones. Based on data from the Framingham Heart Study, increased aortic stiffness was associated with a higher risk of incident hypertension; the initial BP was not independently associated with the risk of progressive aortic stiffening. However, hypertension may contribute to or worsen arterial stiffness, due to increases in distension pressure, vascular thickness and structural stiffening.

Pulsatility
Transcranial Doppler can evaluate the haemodynamics of cerebral blood vessels including the middle cerebral artery. The Pulsatility Index is calculated by subtracting the end-diastolic velocity from the peak-systolic velocity, divided by the time-averaged (mean) velocity. In a study of patients with recent transient ischaemic attack (TIA) or minor stroke, the middle cerebral artery Pulsatility Index was the strongest physiological correlate of leukoaraiosis, independent of age and other variables. It also strongly associated with aortic pulsatility, diastolic BP and aortic stiffness, indicating that cerebral pulsatility depends mainly on...
aortic pulsatility and large artery stiffness, rather than on distal small vessel resistance.

The Reykjavik Study, a large community-based study of older men and women, also found that higher pressure, flow pulsatility and carotid–femoral pulse wave velocity parameters were associated with diffuse microvascular brain lesions, including subcortical infarcts and greater white matter hyperintensity volume, and reduced scores in multiple cognitive domains. It would appear that significant proximal aortic stiffening in older people facilitates transmission of excessive pressure and flow pulsatility into the carotid circulation and that these abnormal pulsatile forces can cause flow-limiting small vessel damage and remodelling, cerebral ischaemia, and reduced cognitive reserve.

**Prognostic value of BP variability**

BP characteristically fluctuates in the short term within a 24-hour period (beat-to-beat, minute-to-minute, hour-to-hour and day-to-night changes) and also in the long term over more prolonged periods (days, weeks, months, seasons and even years). These variations may result from the interaction of environmental and behavioural factors as well as innate changes in cardiovascular regulatory mechanisms.

Based on analysis of data from multiple cohorts of patients with previous TIA or stroke, and patients with hypertension, visit-to-visit clinic BP variability and ‘episodic hypertension’ predicted an increased risk of vascular events, including stroke, myocardial infarction and heart failure, independent of mean BP. BP variability increased with age and is higher in women, those with diabetes, smokers and those with peripheral vascular disease, atrial fibrillation, or previous TIA or stroke.

In analyses of randomised trials of BP-lowering drugs, different drug classes had similar effects on mean BP, but very different effects on visit-to-visit variability. Calcium channel blockers and thiazide diuretics reduce variability whereas β-blockers and ACE/angiotensin II receptor blockers based drugs increase variability. In an analysis of the Anglo-Scandinavian Cardiac Outcomes Trial BP-lowering arm, compared with the atenolol group, the amlodipine group had lower variability of BP from visit to visit, on 24 hours ambulatory BP monitoring and on three measurements within a 10 min clinic visit. Treatment with amlodipine was associated with a lower risk of stroke, but this association was almost completely attenuated after adjusting for within-individual BP variability. The Medical Research Council Trial of BP lowering in older patients with hypertension found similar drug class effects and correlations with outcome.

Antihypertensive drugs should therefore be chosen to reduce variability as well as the mean level, particularly in the setting of stroke prevention. The deleterious impact of BP variability may potentially have implications for neurological conditions associated with dysautonomia, such as Parkinson’s disease, multiple system atrophy and spinal cord trauma. Spinal cord injury at or above T6 may be complicated by autonomic dysreflexia, whereby unmodulated sympathetic reflexes below the injury level generate acute hypertension, often with baroreceptor-mediated bradycardia. Typically, autonomic dysreflexia is precipitated by noxious visceral or somatic stimulation below the level of injury that activates a massive sympathetic reflex, causing widespread vasoconstriction and hypertension. The most common triggers include bladder distension, constipation, pressure sores, fractures or occult visceral disturbances. Hypertensive episodes should be managed by sitting the patient up, removing tight-fitting garments, searching for potential noxious stimuli and using rapid-onset, short-duration antihypertensive agents such as labetalol or nitrates.

**Small vessel disease**

The term small vessel disease encompasses all the pathological processes that affect the small vessels of the brain, including small arteries, arterioles, capillaries and small veins. There are several types but type 1 (arteriolosclerosis) is particularly related to hypertension and also affects the kidney and retina. Pathological type 1 small vessel diseases are characterised by loss of smooth muscle cells from the tunica media, deposits of fibrohyaline material, narrowing of the lumen and thickening of the vessel wall. Postulated mechanisms of cerebral damage include chronic hypoperfusion, acute vessel occlusion, blood-brain barrier damage, local subclinical inflammation and oligodendrocyte apoptosis. The neuroimaging correlates of small vessel disease are deep deep infarcts, cerebral haemorrhages, microbleeds, white matter lesions, dilated perivascular spaces and cerebral atrophy (figure 3 gives an example). Clinical manifestations of hypertension-related small vessel disease include stroke, depression, gait disturbance, cognitive decline and dementia. An acute small vessel occlusion is the cause of about a quarter of all acute ischaemic strokes.

Hypertension is one of the most important risk factors for progression of white matter lesions. Long-term hypertension results in medial lipohyalinosis, thickening of the vessel walls, and narrowing of the lumen of the arterioles and small perforating arteries that supply the deep white matter. From the Rotterdam Scan Study, subcortical white matter lesions were associated with a 1.4 times greater risk of ischaemic stroke while periventricular white matter lesions were associated with 2–3 times excess risk of ischaemic stroke. Deficiencies in gait and balance performance, and urinary urgency also correlate with the severity of these white matter changes.

Frequently associated with white matter lesions, lacunar infarcts are defined as hypointense foci (<15 mm) on MRI T1-weighted sequences, and...
Figure 3  MR scan of the brain of a patient with severe small vessel disease showing (A) Area of restricted diffusion in the right parietal lobe. (B) Periventricular and deep subcortical white matter lesions. (C) Multiple basal ganglia microbleeds.

typically occur in locations such as the basal ganglia, internal capsule, thalamus and pons. The overall prevalence of silent brain infarcts (most of which are lacunar infarcts) is about 28% in the general population. Apart from age, hypertension is the most widely accepted risk factor for silent brain infarcts. Silent brain infarcts also increase the risk of ischaemic and haemorrhagic stroke.

Cerebral microbleeds appear as small, homogeneous round foci of low signal intensity on MRI gradient echo T2 sequences. The prevalence of cerebral microbleeds is 5% in healthy adults, 34% in people with ischaemic stroke and 60% in people with intracerebral haemorrhage. Hypertension-associated cerebral microbleeds are typically located in basal ganglia, thalamus, brainstem and cerebellum, while a lobar distribution is frequently linked to cerebral amyloid angiopathy. The modified Boston criteria help in distinguishing cerebral amyloid angiopathy from small vessel disease, which is more likely to be related to hypertension. Cerebral amyloid angiopathy should be suspected clinically in patients aged over 55 years who have multiple lobar haemorrhages with no obvious alternative cause. Lobar lacunes are also more likely to be associated with cerebral amyloid angiopathy, whereas deep lacunes are more frequent in hypertensive small vessel disease. It can be challenging to manage antiplatelet therapy in patients with cerebral microbleeds as the relative risk of intracerebral haemorrhage increases as the cerebral microbleed burden increases. However, a recent pooled analysis of individual patient-level data has shown that in those with recent TIA or ischaemic stroke, regardless of the cerebral microbleed number, distribution and presence of anticoagulant/antiplatelet treatment, the absolute risk of ischaemic stroke is consistently substantially higher than that of intracerebral haemorrhage. Similarly, in the REStart or STop Antithrombotics Randomised Trial (RESTART), restarting antiplatelet therapy in patients with prior intracerebral haemorrhage did not seem to increase recurrence, even in the presence of microbleeds.

COGNITIVE IMPAIRMENT AND DEMENTIA

Higher BP is associated with smaller total brain volume and reduced regional brain volumes in Alzheimer’s disease brain regions. While the mechanisms underlying these associations are unclear, there is some evidence to suggest that cortical neuronal apoptosis related to subcortical vascular pathology and abnormalities in cerebral blood flow underlie brain atrophy.

In addition to its causal role, the presence of hypertension appears to augment the clinical significance of small vessel disease. The progression of periventricular white matter lesions in patients with hypertension relates to cognitive impairment (especially executive function), whereas there is no association between baseline periventricular white matter lesions and cognitive dysfunction. High home BP and multiple lacunar infarcts are significantly independent predictors for the progression of both cognitive impairment and stroke recurrence. Hypertensive vasculopathy and cerebral amyloid angiopathy may also combine to cause cognitive decline with variable phenotype depending on the location and number of cerebral microbleeds.

Cerebrovascular disease appears to interact with and augment neurodegenerative pathologies. At autopsy, older adults with hypertension have evidence of greater Alzheimer’s disease pathology in the brain, including neurofibrillary tangles and neuritic amyloid-β(Aβ) plaques. Positron-emission tomography studies have shown that the extent of Aβ deposition in the brain is positively associated with higher BP. The duration of hypertension may be a stronger risk factor for cognitive dysfunction than age. Multiple studies have indicated that mid-life hypertension and persistence of elevated BP into late life are leading risk factors for late-life dementia. In contrast, studies of late-life BP suggest that only the extremes of BP (systolic BP >180 mm Hg, diastolic BP <70 mm Hg) increase the risk for dementia.
Large artery disease
Hypertension is an important risk factor for atherosclerosis with a significant dose-response relationship. A 10 mm Hg rise in BP increases the risk of complex aortic atherosclerosis (protruding atheroma, ulcerated plaques, mobiles debris) by about 40% and is highly predictive of ischaemic strokes. Atherosclerotic lesions occur at sites of turbulent flow, such as the carotid bifurcation and cause stroke by releasing fragments with artery-to-artery embolism, or by rupture and/or haemorrhage resulting in acute cerebrovascular occlusions (see an example in figure 4). Carotid atherosclerosis can progress silently with increasing systolic BP and hypertension is also a risk factor for large artery intracranial stenosis.

Patients with hypertension therefore have a high risk of developing large vessel atherothrombotic stroke, which may make them candidates for thrombolytic therapy. However, special considerations apply to BP control in this setting. According to the 2018 American Stroke Association (ASA)/American Heart Association (AHA) guidelines, patients with elevated BP who are otherwise eligible for thrombolysis should have their BP carefully lowered to <185/110 mm Hg and kept <180/105 mm Hg for the first 24 hours after treatment. This recommendation is based on observational studies that higher BPs are associated with greater risk of haemorrhage, but the exact BP at which the risk of haemorrhage after thrombolysis increases is unknown. Treatment options include intravenous labetalol, nicardipine or clevidipine. In patients with BP ≥220/120 mm Hg who do not receive thrombolysis or endovascular therapy, the benefit for starting or restarting hypertension treatment within the first 48–72 hours is uncertain. The guidelines suggest that it may be reasonable to lower BP by 15% during the first 24 hours after onset of stroke.

Importantly, patients with extracranial or intracranial large artery stenoses may require a slower reduction in BP and to a less aggressive BP target, as some degree of BP elevation may be necessary to maintain cerebral perfusion to ischaemic brain regions.

CEREBRAL HYPERTENSIVE EMERGENCIES
Patients with hypertensive emergencies present with significantly elevated BP (usually systolic BP ≥180 mm Hg and/or diastolic BP ≥120 mm Hg) and signs or symptoms of acute target-organ damage. They can develop in patients with or without known pre-existing hypertension. Neurological emergencies account for approximately 30% of patients presenting with severe acute hypertension, and the majority of those who die. Most are due to cerebral infarction with hypertensive encephalopathy and intracerebral haemorrhage accounting for many. About 20%–40% of cases may be attributable to secondary causes and most often consist of renal parenchymal disease and renal artery stenosis.

Hypertensive encephalopathy is defined as an acute organic brain syndrome occurring as a result of failure of the upper limit of cerebral vascular autoregulation. The degree of hypertension necessary to trigger encephalopathy can vary and the rate of BP increase appears to be more important than the absolute BP value with rapidly developing, fluctuating or intermittent hypertension in younger patients, associated with a particularly high risk. It is also associated with poorly controlled hypertension and secondary causes such as immunosuppressive therapy, erythropoietin use and thrombotic thrombocytopenic purpura.

Proposed mechanisms for hypertensive encephalopathy include brain endothelial dysfunction, blood-brain barrier disruption with increased permeability, cerebral oedema and microhaemorrhage formation.

The diagnosis is a clinical one, relying on the presence of neurological symptoms in a patient who is severely hypertensive, supported by additional imaging. Symptoms may include headache, visual disturbance, somnolence, lethargy, partial-onset seizures or generalised-onset seizures. Focal neurological lesions are rare and should raise the suspicion of an acute stroke. If not adequately treated, hypertensive encephalopathy can progress to cerebral haemorrhage, coma and death. Physical examination should focus on cardiovascular as well as neurological assessment. A

**Figure 4** MR scan of brain of a patient with poorly controlled hypertension showing (A) Area of restricted diffusion in the left parietal and temporal lobes. (B) Hyperintense T2 signal change. (C) Severe left internal carotid artery stenosis.
Box 1 Proposed diagnostic studies in patients with suspected hypertensive emergency

Proposed evaluation in patients with suspected hypertensive emergency

History taking
- Symptoms (headache, confusion, somnolence, visual disturbance, seizures, focal neurological deficits).
- Pre-existing hypertension, current treatment, withdrawal, compliance, previous control.
- Over-the-counter medication use (eg, nonsteroidal anti-inflammatory drugs, sympathomimetics).
- Recent corticosteroid exposure.
- Recreational drug use (eg, cocaine).
- Comorbidities (eg, kidney disease, renal artery stenosis).

Diagnostic examination
- BP both arms.
- Radiofemoral delay.
- Signs of heart failure (gallop rhythm, raised jugular venous pulse, bibasal crepitations, peripheral oedema).
- Detailed neurological exam.
- Funduscopy (papilloedema, haemorrhages).
- ECG (ischaemia, arrhythmias, left ventricular hypertrophy).
- Urinalysis (proteinuria, haematuria).

Further investigations as indicated
- Troponin-T, creatine kinase (CK), CK-MB.
- Peripheral blood smear (for assessment of schistocytes).
- Chest X-ray (volume overload).
- Transthoracic echocardiography (cardiac structure and function).
- CT/MRI-brain (intracerebral haemorrhage).
- CT-angiography of thorax and abdomen (acute aortic disease).
- Renal ultrasound (postrenal obstruction, kidney size, asymmetry suggestive of renal artery stenosis).
- Secondary hypertension workup (renal profile, 24 hours urine metanephrines/catecholamines or spot plasma metanephrines, plasma renin and aldosterone, 24 hours urinary cortisol, thyroid-stimulating hormone).

Proposed pathway of evaluation is outlined in Box 1. BP should be measured in both arms and in the lower limbs to detect pressure differences caused by aortic dissection.

Apart from acute BP lowering in patients who had a stroke, there are no randomised-controlled trials that have examined different treatment strategies for most hypertensive emergencies with recommendations instead based on consensus opinion. Large reductions in BP (exceeding >50% decrease in mean arterial BP) have been associated with increased risk of ischaemic stroke and death. Table 1 summarises the most recent recommendations of the European Society of Cardiology. Because patients are often volume depleted as a result of pressure natriuresis, intravenous saline infusion can be used to correct precipitous BP falls if necessary. In patients with hypertensive encephalopathy, intravenous labetalol may be preferable as it leaves cerebral blood flow relatively intact for a given BP reduction compared with nitroprusside.

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiological disorder of heterogenous causes characterised by the sudden onset of neurological symptoms associated with potentially reversible lesions on brain imaging. There is substantial overlap between the clinical syndrome of hypertensive encephalopathy and PRES, and it is unclear whether they represent distinct entities. The pathogenesis of PRES appears to relate to cerebral autoregulatory dysfunction with subsequent dilatation of cerebral arterioles and extravasation of plasma and red blood cells leading to vasogenic oedema. MRI typically shows symmetrical oedema primarily in the cortex and subcortical white matter of the parieto-occipital regions. The lower level of sympathetic innervation in the posterior cerebral arterial circulation may lead to less effective damping of BP oscillations, contributing to the susceptibility to hyperperfusion and vasogenic oedema during acute BP elevation.

Hypertension from renal disease can be a significant cause of PRES, accounting for over 25% of cases in one study of both children and adults, implicating a role for volume expansion or uraemia. There is also a clustering of other well-known risk factors in this population including autoimmune disease, solid-organ transplantation and immunosuppression.

The clinical syndrome, characterised by headache, altered consciousness, visual disturbances and seizures, is identical to that of hypertensive encephalopathy. Unfortunately, there are no established and validated diagnostic criteria for PRES, and it is important to rule out other important differential diagnoses such as posterior circulation stroke and viral or autoimmune encephalitis. A proposed diagnostic algorithm for PRES requires at least one acute neurological symptom (seizure, altered mental state, headache, visual disturbances), one or more risk factors (severe hypertension, renal failure, immunosuppressant drugs or chemotherapy, eclampsia, autoimmune disorder), and neuroimaging with bilateral vasogenic oedema, cytotoxic oedema with patterns of PRES or normal brain imaging; and no alternative diagnosis.

The four most common patterns of brain involvement are the parieto-occipital pattern with vasogenic oedema predominantly in the parieto-occipital lobes, the superior frontal sulcus pattern with oedema mainly along the anterior and media watershed region located in the deep superior frontal sulcus, the
holohemispherical watershed pattern, with oedema located in both anterior and posterior, medial and lateral watershed zones, and the central pattern with vasogenic oedema located predominantly in the deep white matter, basal ganglia, thalami, brainstem and pons.61

The mainstay of therapy is to treat the hypertension with gradual lowering of BP as per the hypertensive emergency guidelines. The offending immunosuppressant or cytotoxic agent should also be stopped if possible. This may require coordinated discussion with other subspecialists (eg, nephrologist, oncologist or rheumatologist) involved in the patient’s care. With removal of the inciting factor and BP control, resolution of findings on neuroimaging within days to weeks is expected. However, occasionally in severe cases, death may result from progressive cerebral oedema, from intracerebral haemorrhage or as a complication of the underlying condition.62 If another immunosuppressive agent is substituted or later started, patients must be monitored closely for recurrence. Avoidance of severe hypertension, fluid overload or progressive injury in this setting will help mitigate risk.

**Haemorrhagic stroke**

Intracerebral haemorrhage accounts for 10%–15% of all strokes in high-income Western countries, but between 20%–50% of those in low-income to middle-income developing countries.63 Hypertensive vasculopathy is the most common cause of spontaneous intracerebral haemorrhage.64 Hypertensive haemorrhages typically occur in the territory of the small penetrating arteries that branch off major intracerebral arteries as they are directly exposed to the pressure of the much larger parent vessel.

The anatomical distribution of microbleeds varies with their aetiology, with hypertensive microbleeds arising in the deep subcortical (figure 5) and infra-tentorial regions, and cerebral amyloid angiopathy-related microbleeds in more superficial lobar regions of the cerebral hemispheres. In a meta-analysis of 28 studies, hypertension was twice as common in patients with deep intracerebral haemorrhage as in those with lobar intracerebral haemorrhage.65 Hypertension has also been shown to be a risk factor for intracerebral haemorrhage in the setting of other underlying causes (eg, cerebral amyloid angiopathy, antithrombotic-associated intracerebral haemorrhage).66

Patients with acute intracerebral haemorrhage should be managed in an intensive care unit or dedicated stroke unit. In the acute phase, they may require intubation and mechanical ventilation, anticoagulation reversal, aggressive BP control, interventions for elevated intracranial pressure and mass effect, treatment for seizures, ventriculostomy or surgical haematoma evacuation.

Severe BP elevation may worsen intracerebral haemorrhage by representing a continued force for bleeding, causing haematoma expansion and potentially worse outcomes. A systematic review of observational studies

---

**Figure 5** A classic example of a hypertensive haemorrhage centred on the left basal ganglia, extending into the left lateral ventricle, with modest dilatation of the ventricles in keeping with early hydrocephalus.
Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on at least two occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive patient AND the new onset of one or more of the following:

- Proteinuria ≥0.3 g in a 24 hours urine specimen or protein/creatinine ratio ≥0.3 (mg/mg) (30 mg/mmol) in a random urine specimen or dipstick ≥+ if a quantified measurement is unavailable.
- Platelet count <100,000/μL.
- Serum creatinine 97.2 μmol/L or doubling of the creatinine concentration in the absence of other renal disease.
- Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory.
- Pulmonary oedema.
- Cerebral or visual symptoms (eg, new-onset and persistent headaches not accounted for by alternative diagnoses and not responding to usual doses of analgesics; blurred vision, flashing lights or sparks, scotomata).

showed that a systolic BP above 140–150 mm Hg within 12 hours of intracerebral haemorrhage was associated with a more than doubling in the risk of subsequent death or dependency. Treatment is a delicate balance as increased BP may be necessary to maintain cerebral perfusion in some patients with intracerebral haemorrhage, and lowering it might cause ischaemia and worsen neurological injury.

For patients with acute intracerebral haemorrhage who present with systolic BP between 150 mm Hg and 220 mm Hg, the US guidelines suggest, based on randomised controlled trials, that acute lowering of systolic BP to 140 mm Hg is safe and may improve functional outcome. Patients with acute intracerebral haemorrhage presenting with systolic BP ≥220 mm Hg require aggressive reduction of BP with intravenous antihypertensive therapy and frequent BP monitoring.

**Eclampsia and pre-eclampsia**

Pre-eclampsia refers to the new onset of hypertension and proteinuria, or hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation (or post partum) in a previously normotensive woman (box 2). It occurs in 3%–8% of all pregnancies. The pathophysiology involves abnormal trophoblast invasion of spiral arteries during placentation leading to placental ischaemia and release of proinflammatory and antiangiogenic placental-derived soluble factors into the maternal circulation.

Eclampsia refers to the development of generalised tonic-clonic seizures in a woman with pre-eclampsia in the absence of other neurological conditions that could account for the seizure. In the UK, recent figures show that 15.5% of direct maternal deaths were due to the hypertensive disorders of pregnancy, and more than half of these women had eclampsia.

Risk factors for pre-eclampsia include prior history, pregestational diabetes, chronic hypertension, systemic lupus erythematosus, antiphospholipid syndrome, body mass index >30, chronic kidney disease, multifetal pregnancy, first pregnancy, family history, prior pregnancy complications associated with placental insufficiency, advanced maternal age and use of assisted reproductive technology.

Patients may present with persistent and/or severe headache, visual abnormalities (scotomata, photophobia, diplopia, amaurosis fugax or rarely transient blindness), upper abdominal or epigastic pain, altered mental status, dyspnoea, retrosternal chest pain. Headache, when present, is a feature of the severe end of the disease spectrum. The pain usually has a throbbing or pounding quality. It can be quite incapacitating and refractory to treatment.

Pre-eclampsia/eclampsia may also cause stroke due to disruption of cerebral autoregulation and alterations in the blood-brain barrier. It is responsible for 36% of pregnancy-associated strokes. Most strokes in this setting are haemorrhagic and preceded by severe and fluctuating BP levels.

Eclamptic seizures develop in 1 in 400 women with pre-eclampsia without severe features and 1 in 50 women with pre-eclampsia with severe features. It has variously been proposed that eclamptic convulsions result from intracerebral haemorrhage, hypertensive encephalopathy, cerebral oedema or vasospasm. Different mechanisms may be operating in different patients, with the compounding effects of cerebral hypoxia, intravenous fluid and drug administration, and varying degrees of hypertension.

For women with pre-eclampsia at ≥37 weeks of gestation, even with no features of severe disease, delivery is recommended. If there are features of severe disease, then delivery at ≥34 weeks of gestation after maternal stabilisation is indicated. When there is no evidence of serious end-organ dysfunction, an expectant approach with close monitoring is reasonable to achieve further fetal maturity. However, at any gestational age, evidence of severe hypertension, serious maternal end-organ dysfunction or non-reassuring fetal monitoring tests are generally an indication for urgent delivery.

BP should be measured daily at home in patients being managed expectantly with pre-eclampsia without severe features and at least twice weekly in clinic. Antihypertensive therapy should be initiated if there is persistent systolic BP ≥150 mm Hg or diastolic BP ≥100 mm Hg. Intravenous labetalol or hydralazine are the recommended first-line agents for acute therapy of severe hypertension. Magnesium sulfate is the drug of choice for the prevention of eclampsia.
Women with a history of pre-eclampsia have a twofold to fourfold increased risk of cerebrovascular disease and stroke later in life and thus pre-eclampsia has being identified as an important sex-specific risk factor for stroke by the American Heart Association/ American Stroke Association guidelines. In the California Teachers Study, this excess stroke risk appeared to be reduced by long-term aspirin use. The increased risk of cerebrovascular disease in women with prior pre-eclampsia is also associated with subjective cognitive complaints and increased white matter lesion burden on MRI, suggestive of a continued susceptibility to brain injury that persists after pregnancy.

SLEEP-DISORDERED BREATHING AND HYPERTENSION

Sleep-disordered breathing is an umbrella term for a constellation of sleep-related breathing disorders including obstructive sleep apnoea, central sleep apnoea, both with and without Cheyne–Stokes respiration, and sleep-related hypoventilation.

Typical symptoms of obstructive sleep apnoea include excessive daytime sleepiness, frequent awakenings during sleep, snoring, reduced concentration and impaired memory. Risk factors include increasing age, male gender, obesity, craniofacial and upper airway soft tissue abnormalities, and certain medical conditions (pregnancy, heart or renal failure, prior stroke/TIA, hypothyroidism).

Approximately 50% of patients with obstructive sleep apnoea in turn have hypertension. Obstructive sleep apnoea was associated with a 2.2-fold increased risk of incident ischaemic stroke in this population. Although it is likely that patients are still underinvestigated for sleep-disordered breathing poststroke, there is at least an increasing awareness that it is associated with worse outcomes including increase risk of recurrence, and worse functional and cognitive function at 90 days poststroke.

CONCLUSIONS

Neurologists frequently bear witness to the consequences of untreated and uncontrolled hypertension, in the form of acute stroke and in memory or sleep clinics, and more rarely, in the emergency department with the patient with encephalopathy. Early diagnosis of hypertension with regular monitoring and treatment is essential to promote and sustain brain health.
2 Ghali MGZ. The brainstem network controlling blood pressure: an important role for pressor sites in the caudal medulla and cervical spinal cord. J Hypertens 2017;35:1938–47.


REVIEW


