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RESEARCH ARTICLE

Neuroimaging Findings in Symptomatic Hypertensive Encephalopathy

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ABSTRACT

To assess the relevance clinicians and radiologists assign to making hypertension (HTN) explicit in acutely symptomatic subjects admitted for either stroke, confusion or cognitive deficit, a revision was carried out of cases discussed in our institution in the last eleven years, at either the Neuroradiology-Stroke or the Neuropsychiatry multidisciplinary meetings (MDTs). Consistency of the provided clinical information and radiological findings concerning HTN were checked in 11810 subjects (Group 1), since both influence neuroimaging interpretation, diagnosis and management.

Similar information was collected in a subgroup of 25 subjects (Group 2), with signs of stroke included in Group 1 in whom there was pre-existent history of severe HTN, who were evaluated with multimodality neuroimaging in 48 hours from admission and who had improved clinically in 72 hours.

The word "hypertension" included in the initial neuroimaging request, blood pressure (BP) levels on admission, radiology reports describing intra axial bleed, mentioning "hypertensive encephalopathy", "chronic hypertensive encephalopathy", "hypertensive microbleeds", "amyloid microbleeds", features and quantification of cerebral small vessel disease (CSVD), a non-specific pattern of cortical atrophy, dolicoarteriopathy, presence and degree of carotid or vertebrobasilar stenosis were tabled.

Electronic records of blood pressure (BP) were available in 10003/11810 cases and in written notes in 1807/11810; 1582/11810 were not hypertensive and 8421/11810 hypertensive. Imaging requests did explicitly include the word "hypertension" in 1184/11810.

Radiology reported acute intracranial bleed on admission in 1516/11810, hypertensive encephalopathy in 248/11810, chronic hypertensive encephalopathy in 148/11810, hypertensive-type microbleeds in 295/11810, amyloid-type microbleeds in 390/11810, SVD features without quantification in 1554/11810, SVD 1/3 in 577/11810, SVD 2/3 in 1402/11810, SVD 3/3 in 776/11810, non-specific cerebral atrophy in 800/11810, vessel tortuosity in 128/11810 and significant carotid or vertebrobasilar stenosis in 1292/11810 of cases. On neuroimaging revision, one or more HTN features were found in 10311/11810 cases.

In group 2 mean systolic BP on admission was 193mmHg, diastolic 104mmHg, age 55 years, 15/25 had PRES, 7/25 acute on chronic hypertensive encephalopathy, 2/25 CAA and 1/25 normotensive PRES. HTN findings were reported in 22/25 cases.

Results suggest an initial underestimation of HTN by both referrers and radiologists in acutely symptomatic subjects, later identified and characterised when reviewed and discussed at MDTs.

Introduction

Arterial HTN (HTN) is defined by a systolic blood pressure at or above 140mmHg, and/or diastolic blood pressure at or above 90mmHg, and/or taking antihypertensive medication [1]. The size of affected subjects aged 30-79 doubled in the 29-year interval between 1990 and 2019 [2]. It is considered by some authors as what accounts for 6% of adult deaths throughout the world [3], the global leading cause of death of 10.4 million people per year [4, 5]. Its incidence is increasing, particularly associated to acute stroke, a devastating clinical condition with high morbidity and mortality[6, 7].

More than half of those suffering from HTN have additional cardiovascular risk factors including diabetes, dyslipidaemia, overweight/obesity, hyper uricaemia and metabolic syndrome, as well as unhealthy lifestyle habits such as smoking, high alcohol intake and sedentary lifestyle[8].

Severe increases in blood pressure (BP) are high risk cardiovascular conditions in which there is HTN-mediated organ damage [9] to the heart [10], brain, retina, kidneys and large arteries [11] with different clinical presentations including stroke, pulmonary oedema and coronary syndromes as the most frequently seen in Emergency Departments. The causes of organ damage are not only the haemodynamic injury in itself, but also the superimposed inflammatory changes triggered by elevated BP including complement activation resulting, in some organs as the kidneys, in histopathological features similar to other conditions in which there is such activation, as malignant nephrosclerosis and atypical haemolytic uraemic syndrome[12].

The brain is a highly perfused organ receiving 20% of the cardiac output in normal conditions, with a self-regulated circulatory system, described by Bayliss more than a hundred years ago [13], intended to ensure a constant blood flow to maintain its high metabolic rate[14]. Cerebral blood flow (CBF) is kept constant within a systolic BP range between 60 and 160mmHg[15], although the upper and lower limits are shifted to higher levels in subjects suffering from chronic HTN [16] when compared to normotensive patients and also on animal experimental models[17,18]. If systolic blood pressure exceeds the upper self-regulatory limit, CBF becomes linearly dependent on arterial pressure drastically increasing the risk of brain injury[19].

The cerebral vascular architecture has a superficial and a deep system. In the former, there are pial vessels and penetrating arterioles with multiple anastomoses, surrounded by CSF in the surface of the brain. In the latter, there are penetrating arteries turning into parenchymal arterioles as they go deeper within the tissue, being then fully surrounded by astrocytes [20]. There are morphological and functional differences between both systems. The pial arteries have extrinsic innervation from the peripheral nervous system and the parenchymal arterioles have intrinsic innervation by the neuropil. In the deep system there is a single circumferential layer of smooth muscle not responding to neurotransmitters that on the other hand have a conspicuous effect over the superficial system, such as serotonin and norepinephrine [21]. Pial vessels are richly anastomosed with a collateral network while parenchymal arterioles tend to be long and not branched hence more susceptible to ischaemic damage[22].

The brain has a dense and profusely intercommunicated network of capillary vessels. Its primary flow regulator is the pressure gradient between the precapillary arteriole and postcapillary venule, with a velocity ranging 0.3 to 3.2 mm/sec [23] [24]. The capillary density varies between grey and white matter, physiological and pathological conditions. Among the latter, chronic hypoxia increases the capillary network density while HTN decreases it, as it does in in the case of peripheral tissues, what tends to increase vascular resistance [25, 26, 27] contributing to end organ damage [28]. When regulatory mechanisms of cerebral blood flow are impaired detrimental effects appear, including increased permeability of the blood brain barrier (BBB) and subsequent vasogenic oedema[27] as seen in acute and acute on chronic hypertensive encephalopathy. HTN related BBB breakdown is due to inflammation, oxidative stress and vasoactive circulating molecules, which expose cerebral tissue to cytotoxic compounds causing neuronal loss, cognitive decline and impaired recovery from ischaemia[29,30].

HTN during midlife increases risk of morphological and functional brain changes later in life, when identifying them may better represent previous long-term exposure to increased blood pressure than the measurement itself due to hypertensive treatment and vessel ageing[31, 32].

Untreated HTN causes pathological alterations in the cerebral macro and microcirculation including

cerebral micro vessels altering vascular structure, network architecture and function, subsequently leading to white matter injury [33], micro haemorrhages and lacunar ischaemic infarcts, which may have devastating consequences in the Central Nervous System (CNS), particularly in subjects with unrecognized hypertensive disease or those resistant to treatment[34]. These changes in the brain parenchyma, characterised as CSVD, are associated with distal leptomeningeal and intracerebral vessel pathology[35], one of the most prevalent pathological processes found by neurologists and an important cause of stroke and dementia. Although HTN is not the only causative factor of CSVD it is the most frequent of its aetiologies[36, 37].

HTN is the leading cause of a cerebral long-term micro-vasculopathy identifiable on histopathology, although not with the current neuroimaging techniques available in clinical settings. However, cross-sectional imaging can identify the main surrogate markers of CSVD in the brain parenchyma, the most frequent of which are punctate, patchy or confluent white matter abnormalities [38], assessable on computed tomography (CT) and magnetic resonance imaging (MRI), and microbleeds, identifiable on haemoglobin-sensitive MRI sequences.

CSVD parenchymal injuries encompass a spectrum of morphological changes in the brain caused by endothelial dysfunction [39] and damage to the blood brain barrier. Post mortem exams in hypertensive subjects have shown a combination of microscopic changes in the arteriole walls including fibrinoid necrosis, microaneurysms, hyalinosis, microatheromas, luminal stenosis and dilated perivascular spaces[13]. Their subsequent associated macroscopic abnormalities include diffuse damage to the white matter, microbleeds, cortical microinfarcts, subcortical lacunar infarcts, dilatation of the Virchow-Robin spaces, atrophy and vascular deformities [15], all of which can be assessed, characterised and quantified by neuroimaging, particularly CT and MRI.

CSVD may be caused by several other entities besides HTN, including cerebral amyloid angiopathy (CAA), congenital diseases, inflammatory pathology and a miscellaneous group of conditions including post-radiation angiopathy and non-amyloid microvessel degeneration [40]. However, the most frequent causes of CSVD are hypertensive vasculopathy and cerebral amyloid angiopathy, each one of which present different neuroimaging features. Hypertensive vasculopathy findings include white matter abnormalities and microbleeds with a distribution pattern in the basal ganglia, thalami, brainstem and cerebral lobes, microinfarcts in thalamocapsular areas and vascular changes in the penetrating arterioles in the brain parenchyma; superficial haemosiderosis is seldom present in hypertensive disease of the brain. Cerebral amyloid angiopathy shows microbleeds and microinfarcts predominantly distributed in the cerebral lobes, with patchy foci of superficial cortical haemosiderosis and infrequent lacunar infarcts[13,41]. Both forms may appear combined, showing a mixed pattern of changes usually distinguishable on current neuroimaging techniques in daily clinical practise.

The relationship between HTN, as one of the main cardiovascular risk factors, and white matter lesions (WML), favours the latter as a surrogate macroscopic marker of CSVD[42,43,44,45], particularly given the typical distribution pattern of microbleeds, an additional surrogate marker of CSVD with an incidence increasing with age [46], allowing to differentiate CAA from hypertensive related WML.

Methods

The study was approved by the Divisional Board as a Clinical Audit and Quality Improvement Project and registered as RN973340.

The main purpose of this study was to assess the relevance clinicians and radiologists assign to making HTN explicit when the former request neuroimaging studies for symptomatic patients in cases of stroke, confusion or acute cognitive deterioration and when the latter describe HTN related findings in their reports of those exams.

In our institution, neuroimaging protocols for the conditions leading to identify features of hypertensive encephalopathy include non-enhanced CT (NECT) for acute haemorrhagic stroke; NECT for ischaemic stroke in subjects with known time of onset within thrombolysis window, followed by CTA of the neck and head; NECT, CTA and PCT of the head for stroke patients with an unknown time of onset or candidates for mechanical thrombectomy; MRI of the head with MRA of the neck and head for patients with a transient ischaemic event (TIA), NECT or MRI for subjects with suspected cognitive impairment (table 1).

Table 1: Neuroimaging protocols in symptomatic subjects.

Referral condition on admission	Imaging Procedure
Haemorrhagic stroke	NECT
Ischaemic stroke	NECT, CTA
Stroke with unknown time of onset	NECT, PCT, CTA
Eventual Thrombectomy in ischaemic stroke	NECT, PCT, CTA
TIA	MR, MRA
Rapid cognitive deterioration	NECT, MR
Cognitive impairment	MR

Current CT scanners permit to obtain in very few seconds a common NECT or, preferably, a dual energy (DECT) of the head, a technique providing higher sensitivity [47] to detect acute and chronic vascular related changes, within minutes of admission and usually reported within the hour, to rule out acute or chronic intracranial bleed, mass effect, direct or indirect signs of acute ischaemic stroke, diffuse cerebral oedema and all relevant features characterising CSVD.

Concerning the clinicians, the information provided when requesting neuroimaging studies of acutely symptomatic patients and, for the radiologists, their description of HTN related findings were prospectively assessed and retrospectively reviewed in cases discussed at Neuroradiology-Stroke and Neuropsychiatry Multidisciplinary Meetings (MDTs) in the last 11 years at our institution. The included cases were called Group 1.

An additional purpose of this study was to assess the same in a subgroup of subjects from Group 1 in whom there was a documented pre-existent history of severe HTN and were evaluated with multimodality imaging within 48 hours of admission; including CT, perfusion CT (PCT), CT angiography (CTA) and MRI. Consistency of radiology reports of the different exams was also assessed. The included subjects were called Group 2.

Hypertensive-related radiological information was prospectively collected from imaging studies performed on symptomatic subjects discussed at the Neuroradiology-Stroke and Neuropsychiatry MDTs by an experienced radiologist, and retrospectively reviewed by three and also experienced radiologists as part of the Quality Improvement Project (QIP) mentioned above, intended to standardise description and quantification of findings attributable to HTN in neuroimaging reporting.

Symptomatic subjects were considered those with an acute stroke, transient ischaemic attack (TIA), confusion, and/or rapidly deteriorating cognitive functions. The period of data collection extended between January 2012 and January 2022. Neuroimaging studies included head CT, CTA of the head and neck, head MRI and MRA of the head and neck, and Doppler Ultrasound of the neck vessels. The clinical information provided by physicians when requesting the initial study was also considered.

The tabled variables comprehended the explicit mention of HTN among the details sent by the referring clinician when requesting the initial neuroimaging study and blood pressure levels on admission from the records. Variables from the radiology reports included description of intracranial macrobleeds, presence of CSVD and its severity in the Fazekas scale, presence of microbleeds, their number according to the Boston scale and the distribution pattern, the explicit mention of hypertensive encephalopathy, chronic hypertensive encephalopathy, lacunar infarcts, vessel tortuosity or dolichoangiopathy, presence and significance of large vessel stenosis, and consistency between the report and the outcome of the MTD discussion reflected by the consensus opinion and the clinical working diagnosis.

Weekly MDTs take place in our Department of Radiology attended by an experienced consultant radiologist and also experienced clinicians from Stroke Medicine and an additional MDT with Psychiatrists and Psychologists, to discuss clinical and neuroimaging findings in symptomatic subjects of their respective areas, as a routine Clinical Governance procedure to ensure inter departmental consensual opinions, agreed clinical approach and clinical working diagnoses. The list

of patients for discussion is sent to Radiology the day before to review each case, pre-existent radiology reports, findings and to carry out, if necessary, additional post processing subsequently sent onto PACS for documentation purposes. Discussions during the meeting are subsequently documented in the electronic records and also in the radiology informatics systems, which can be assessed during admissions or retrospectively by relevant members of the health care team. If disagreements or discrepancies on neuroimaging findings arise, the corresponding study is sent for discussion at the Department of Radiology Events and Learning Meetings (REALM) according to the Royal College of Radiology Standards[48], to ensure a consensus opinion among the Consultant Radiologists, reflective learning or request an external imaging revision if required. REALM discussions are documented in an ad hoc departmental archive and addenda are entered to the radiology report if clinically necessary.

Results

Group 1 comprised 11810 cases and Group 2 included 25 subjects.

BP records were available electronically in 10003 cases and were only in the written notes in 1807/11810 cases (graph 1). There were 1582/11810 (16%) non-hypertensive and 8421/11810 (84%) hypertensive subjects. Imaging requests did explicitly include the word "hypertension" in 1184/11810 (10%) patients (graph 1).

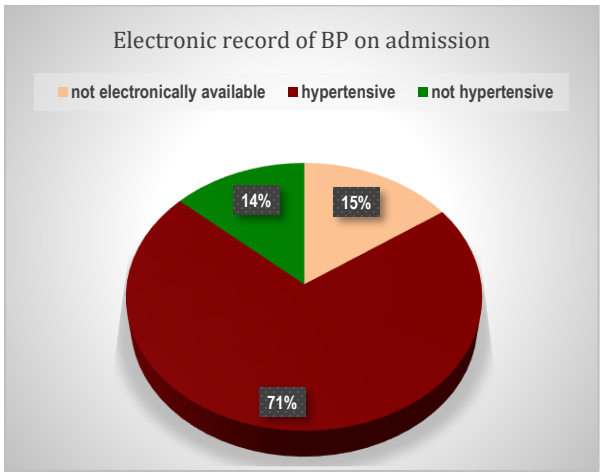
Radiology reports (graph 2) described haemorrhagic stroke on admission in 1516/11810 (13%) of the cases, hypertensive encephalopathy in 248/11810 (2%), chronic hypertensive encephalopathy in 148/11810 (1%), a hypertensive-type pattern of microbleeds in 295/11810 (2%), an amyloid-type pattern of microbleeds in 390/11810 (3%), SVD features were described but not quantified in 1554/11810 (12%), quantified as SVD 1/3 in 577/11810 (5%), SVD 2/3 in 1402/11810 (12%) and SVD 3/3 in 776/11810 (7%). A non-specific pattern of cerebral atrophy was mentioned in 800/11810 (7%), dolicoarteriopathy in 128/11810 (1%) and a significant degree (≥50%) of carotid or vertebrobasilar stenosis in 1292/11810 (11%) of cases.

When imaging studies were prospectively reviewed in preparation for the MDTs, and when discussing the cases or retrospectively when documenting the discussion, no discrepancies were found in the cases of haemorrhagic stroke. However, one or more hypertensive-attributable radiological features were present and not reported in 10311/11810 (87%) cases (graph 3). The least frequently omitted was CSVD (discrepancies in 53% of the cases) and the most frequently omitted were dilated VRS, atrophy and dolichoangiopathy (86% of discrepancies).

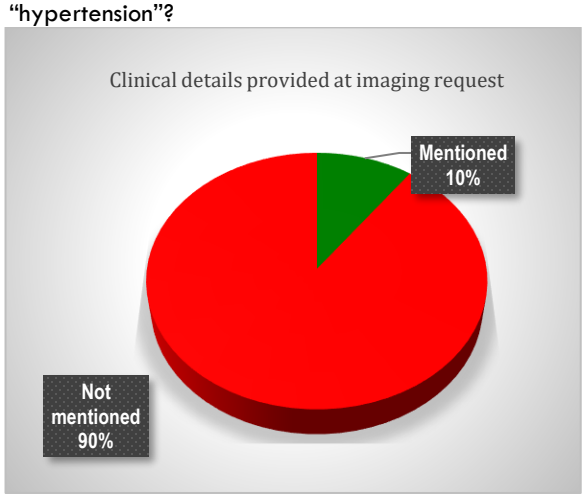
In Group 2 the average systolic pressure on admission was 193mmHg, diastolic 104mmHg, average subjects age was 55 years, 15/25 showed features of PRES, 7 acute on chronic hypertensive encephalopathy, 2/25 CAA and 1/25 normotensive PRESS. Consistent findings attributable to HTN were reported in 22/25 cases (graph 4). In a subject with acute on chronic hypertensive encephalopathy with diffuse swelling of the brainstem, suspicion of malignancy in the pons was reported as main differential diagnosis. In this case, BP levels, substantially elevated, had not been included in the clinical information provided to radiology, very probably influencing the provided radiology report.

Graph 2: information expectable from clinicians when requesting imaging studies in hypertensive subject

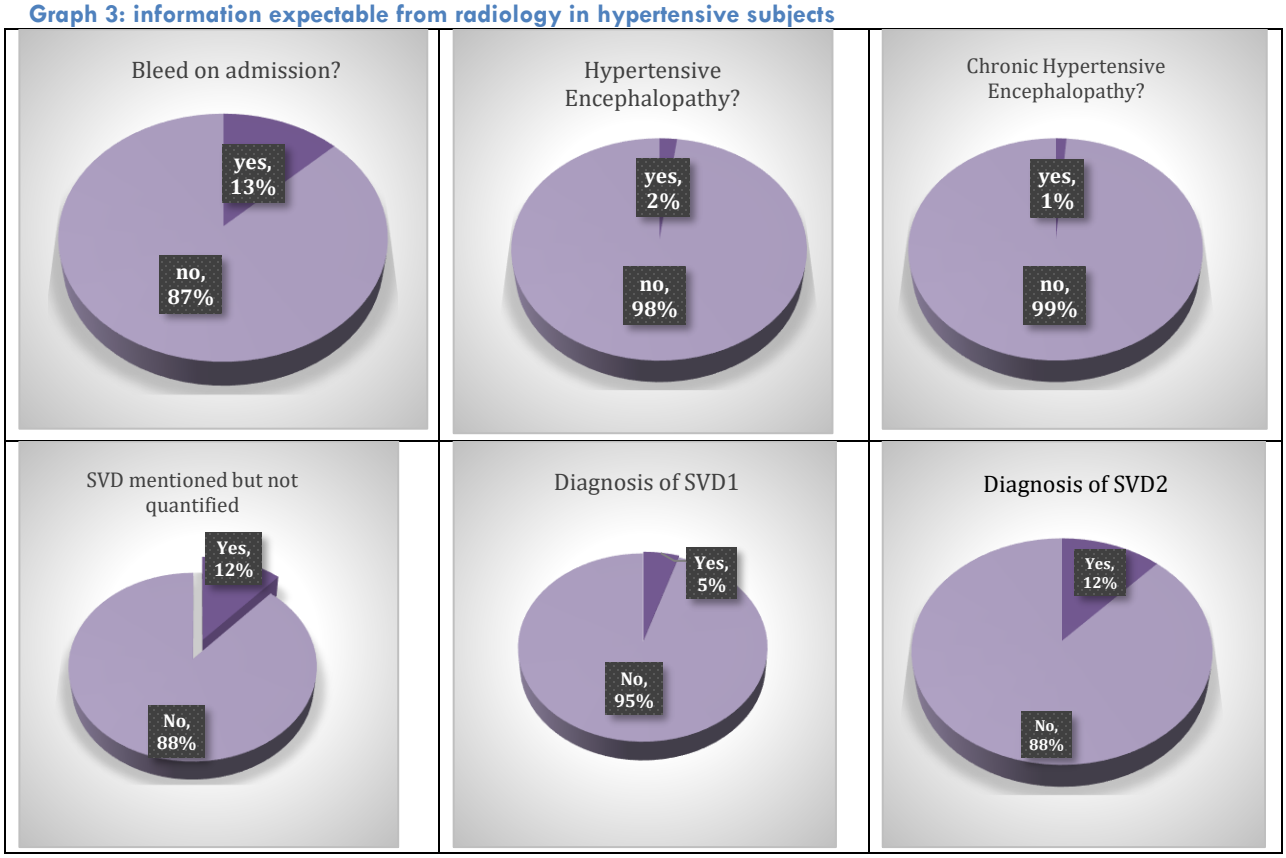
BP measurement on admission?

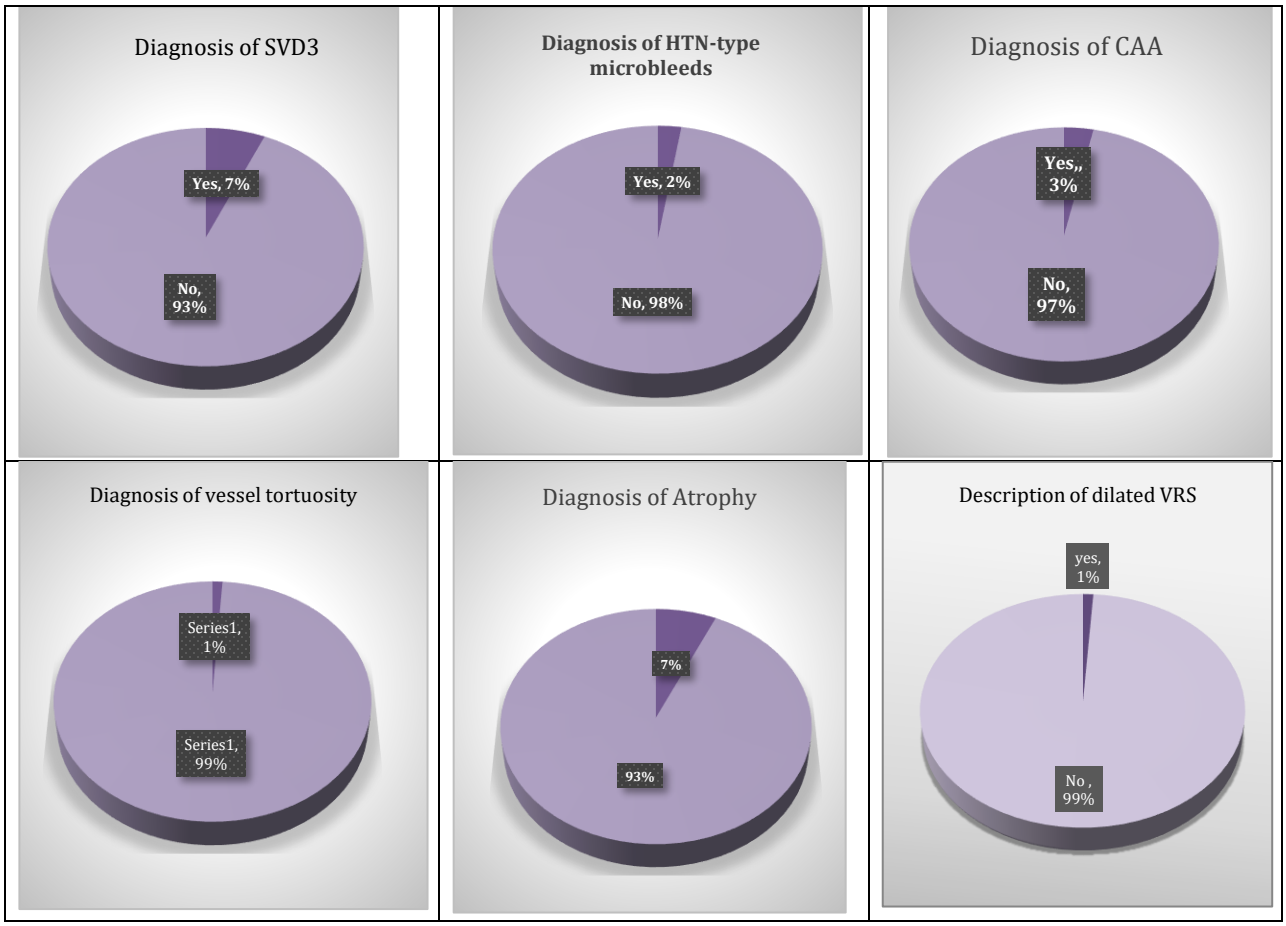


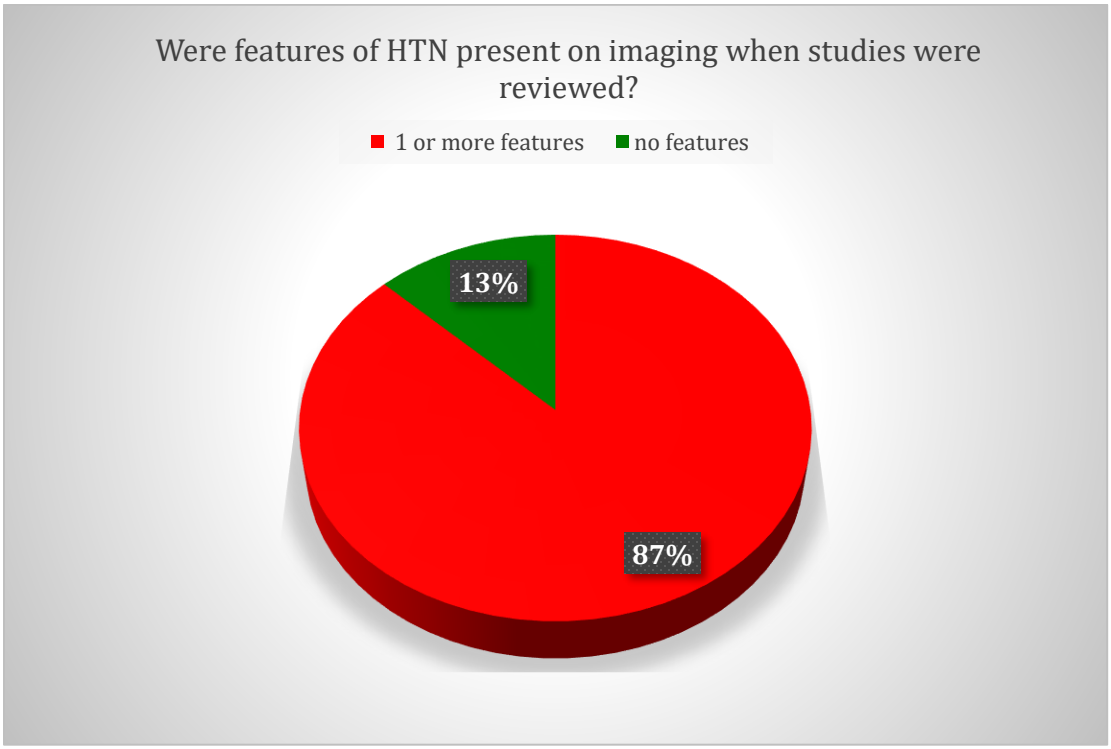
Did clinicians when requesting neuroimaging mention "hypertension"?



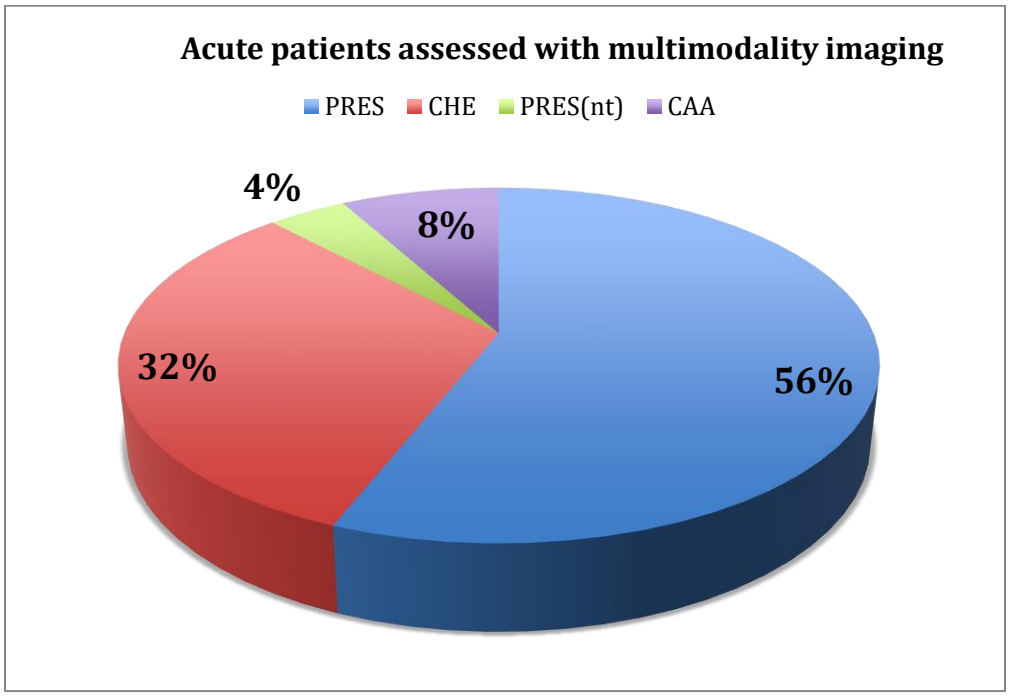
Graph 3: information expectable from radiology in hypertensive subjects







Graph 3: Results in 11810 subjects



Graph 4: multimodality neuroimaging findings within 48 hours from admission in 25 hypertensive subjects with acute signs & symptoms

Discussion

Neuroimaging: the key to identify HTN related abnormalities.

Acute hypertensive syndromes on Neuroimaging: Posterior reversible encephalopathy (PRES), Malignant HTN, Acute on chronic HTN encephalopathy and chronic HTN encephalopathy.

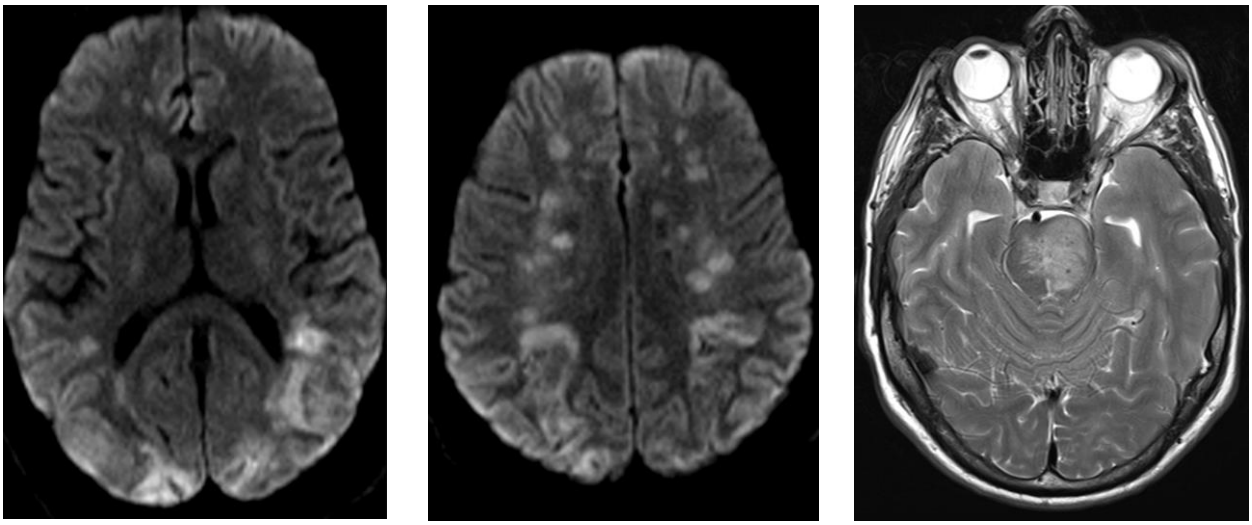
BP at or above 180/120mmHg with end organ dysfunction define acute hypertensive crises, at which failure of the circulation's self-regulatory mechanisms in the brain lead to endothelial dysfunction and acute hypertensive encephalopathy [49] , frequently presenting with headache, epistaxis, faintness, psychomotor agitation, neurological deficit, chest pain and dyspnoea[50].

Osborn distinguishes different acute hypertensive encephalopathy presentation forms on neuroimaging, which include acute posterior reversible encephalopathy syndrome (PRES), malignant HTN, accelerated HTN, acute on chronic and chronic HTN encephalopathy[51].

1. Acute hypertensive encephalopathy or PRES

PRES is the most common manifestation of acute hypertensive encephalopathy, also known as Reversible Posterior Leucoencephalopathy Syndrome, which develops in subjects with HTN, blood pressure fluctuations, renal failure, immunosuppression, autoimmune conditions and eclampsia[52]. As a clinical syndrome, PRES includes subcortical vasogenic oedema, not always reversible, distributing predominantly in parietooccipital lobes, although not in all cases. It may involve the posterior fossa and cervical cord. Some of the subjects suffering from it evolve to stroke and intracranial bleed. Although its pathophysiology is not completely understood, HTN and endothelial damage tend to be almost always present [53] ; however, it may occur in normotensive subjects[54,55,56].

Typical MRI findings include geographical areas of vasogenic oedema, hypointense on T1 and hyperintense on T2/FLAIR. The pattern tends to be symmetrical, predominantly distributed in the posterior circulation and may show punctate haemorrhagic foci on susceptibility-weighted images (T2*), which tend to resolve in matter of days. The most common topographical distribution of neuroimaging abnormalities in subjects with PRES is parietooccipital (Fig 1a); however, additional patterns include superior frontal sulcus, whole hemispheric watershed (Fig 1b), cerebellar, brainstem (Fig 1c) and spinal[57,58,59].



1a 1b 1c

Figure 1: PRES. 1a: 41-year-old male with typical presentation with fairly symmetrical foci of vasogenic oedema. 1b: 52-year-old female with foci of vasogenic oedema with whole hemispheric distribution. 1c: 42-year-old male with vasogenic oedema in the brainstem.

Since clinical presentations often start with seizures and severe headache, the most common imaging assessment is carried out with non-enhanced CT (NECT) which tends to be normal or show very subtle findings not always identified. In these cases, if admission CT is normal and PRES is clinically suspected, MRI including diffusion weighted series (DWI-ADC) and haemoglobin sensitive sequences or T2* should be carried out[60].

The main differential diagnoses include acute ischaemia, vasculitis, status epilepticus, venous thrombosis, reversible vasoconstriction syndrome, hypoglycemia and thrombotic microangiopaties secondary to systemic conditions such as thrombocytopenic purpura, disseminated intravascular coagulopathy and haemolytic-uremic syndrome. Ischaemic stroke is usually confined to a vascular territory; vasculitis tends to be less symmetrical, scattered and random in distribution, enhancing after the intravenous injection of contrast; status epilepticus shows unilateral foci; thrombosed venous sinuses lack flow void on T2-FLAIR, are hyperintense on T1 and well depicted on CT venogram (CTV); reversible vasoconstriction syndrome tends to be more confined; thrombotic microangiopathies are challenging as they may frequently present with PRES[51].

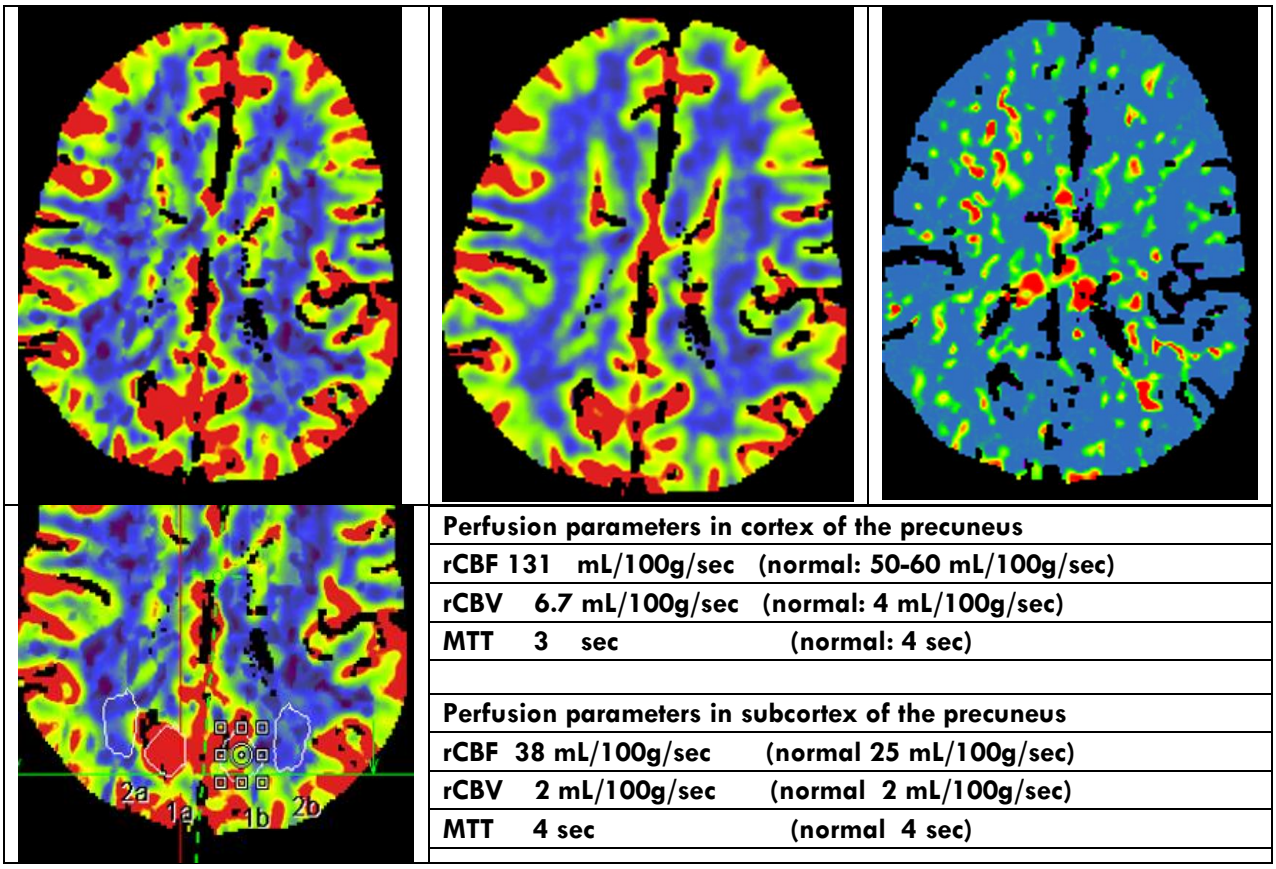
2. Malignant HTN

Malignant HTN is a life-threatening condition, which develops in acute hypertensive crises triggered by an abrupt increase in blood pressure leading to end organ damage[61], which in the brain causes patchy or confluent areas of cerebral vasogenic oedema and in the eyes retinal exudates, haemorrhages or papilledema [62, 63]. According to Osborn, a subtype of malignant HTN with severe retinal changes but no papilledema may be called accelerated HTN[51]. A rapid control of the hypertensive crisis within a few hours is of paramount importance[64] in malignant HTN.

Although it may be seen in previously normotensive subjects, it tends to develop in individuals with poorly controlled chronic HTN or recent cessation of antihypertensive treatment [65]. It can also develop in patients with pheochromocytoma, substance abuse [66, 67] and autonomic hyperactivity[68].

Imaging features include those seen in PRES, tend to involve brainstem and watershed areas, show diffuse damage to the blood brain barrier on post contrast series and foci of restricted diffusion on DWI-ADC. Abnormal perfusion values are noted on PCT (Fig 1)

The main differential diagnosis of malignant HTN (mHTN) is PRES, in which no papilledema, retinal exudates or haemorrhages tend to be present and ophthalmic manifestations, if seen, usually improve[69].



Perfusion parameters in cortex of the precuneus	
rCBF 131	mL/100g/sec (normal: 50-60 mL/100g/sec)
rCBV 6.7	mL/100g/sec (normal: 4 mL/100g/sec)
MTT 3	sec (normal: 4 sec)
Perfusion parameters in subcortex of the precuneus	
rCBF 38	mL/100g/sec (normal 25 mL/100g/sec)
rCBV 2	mL/100g/sec (normal 2 mL/100g/sec)
MTT 4	sec (normal 4 sec)

Figure 2: abnormal perfusion pattern in malignant HTN with high cortical rCBF values, increased rCBV and preserved MTT. Perfusion parameters in the subcortical white matter are much closer to normal

3. Acute on Chronic Encephalopathy

Within the spectrum of neuroimaging patterns in hypertensive encephalopathy an additional subgroup was identified in the universe of subjects discussed at neuroradiology stroke and neuropsychiatry multidisciplinary meetings in the last ten years, consistent with Osborn's description[51]. It included middle-aged adults having longstanding poorly controlled chronic idiopathic HTN, generally not compliant with the prescribed therapy, in whom extensive chronic brain damage attributable to HTN to which acute hypertensive episodes superimposed (Fig 2 & 3). The subjects self-referred, presenting with some periodicity to the general practitioner's clinic or the Emergency Department with headache, increasing confusion, drowsiness, no seizures or papilledema or acute retinal changes and no acute neurological deficit. Neuroimaging showed patchy white matter hypointensities and brainstem swelling on CT, PCT with increased relative cerebral blood flow (rCBF) in the cortex, decreased relative cerebral blood volume (rCBV) in the subcortical and deep white matter and no territorial perfusion delay on mean transit time (MTT). Geographical non-territorial areas of vasogenic oedema with scattered smaller foci of cytotoxic oedema on diffusion-weighted images, a degree of brainstem swelling and a myriad of microbleeds all appeared.

In these subjects, clinical signs/symptoms and acute neuroimaging abnormalities slowly resolved in a matter of days or weeks once HTN could be controlled, followed by a degree of cerebral atrophy developing in a period of a couple of years after the acute admission. No large vessel occlusion and no signs of vasculitis or CADASIL were identified in this subgroup of subjects in whom the clinical working diagnosis was acute in chronic hypertensive encephalopathy.

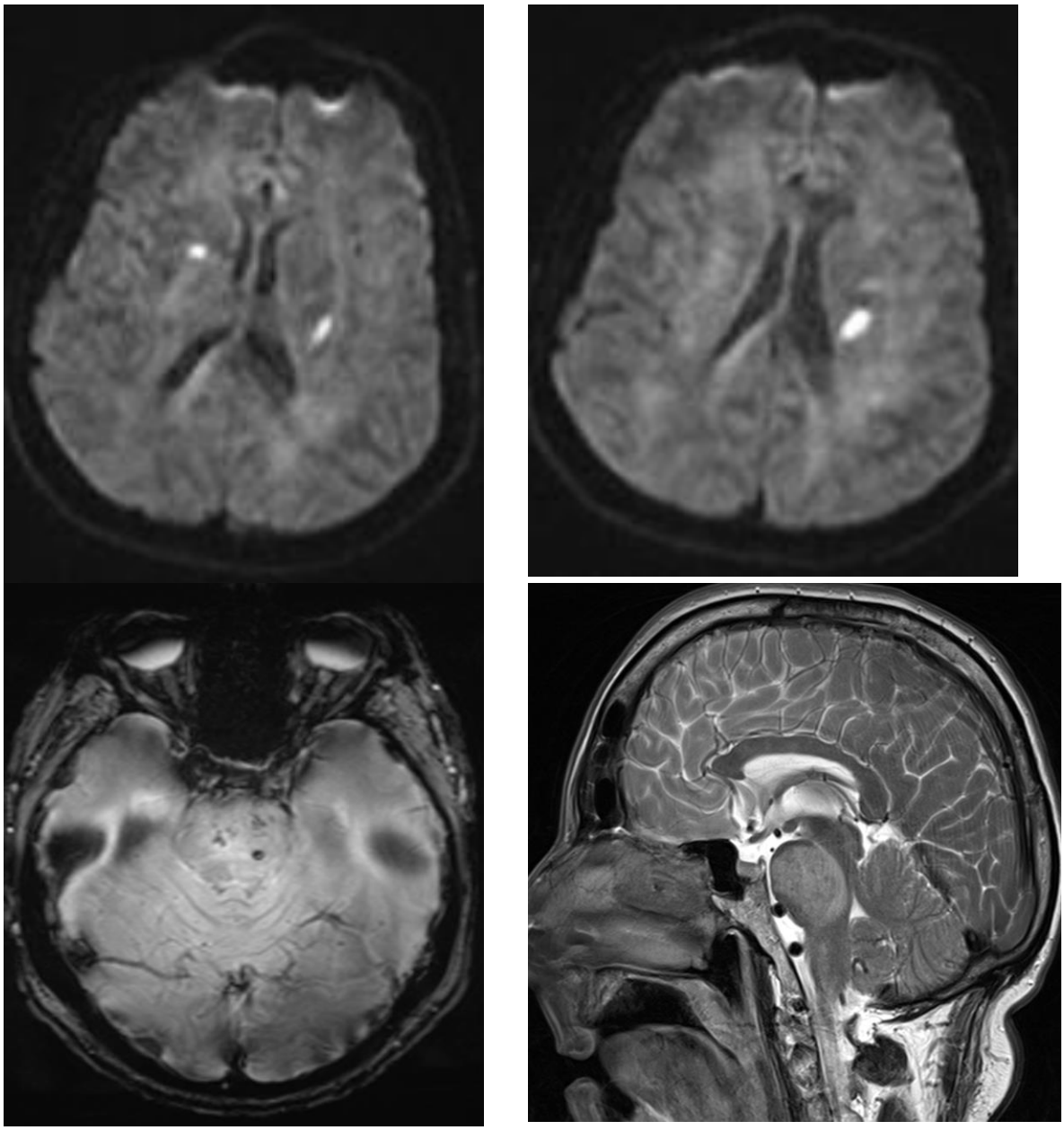


Figure 3: Acute on chronic hypertensive encephalopathy in a 45-year-old male with DWI changes in the brainstem and watershed areas, microbleeds, brainstem swelling, abnormally high cortical perfusion values, intact long descending tracts and typical spectra

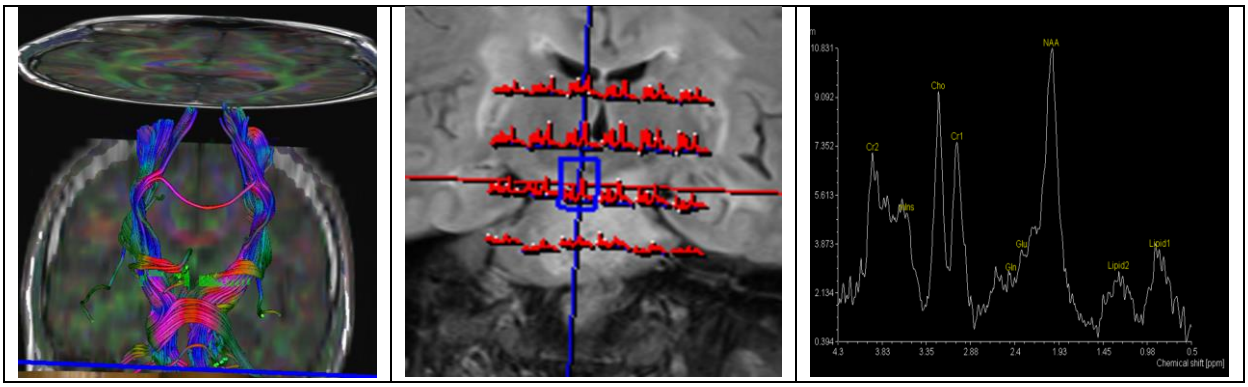


Figure 4: Acute on chronic hypertensive encephalopathy. See fig 2 caption

4. Chronic Hypertensive Encephalopathy.

Chronic changes in the brain in HTN subjects may be identified incidentally, if asymptomatic, or present with confusion, seizures, TIA, cognitive deterioration or episodes of acute on chronic HTN encephalopathy. Neuroimaging features include white matter changes [70], microbleeds, lacunar infarcts, dilatation of VR spaces, cortical atrophy and dolichoangiopathy, all of which can and should be assessed and quantified on neuroimaging[71,72] (Table 2). Other causes of SVD include CAA, diabetes, Alzheimer's disease, Fabry's disease, MELAS and vasculitis[73]. Chronic HTN is, however, the most common cause CSVD[74] due to endothelial dysfunction, arteriole wall thickening, hyalinosis, stenosis and vessel occlusion [75], which decrease oligodendrocyte density, myelin changes, gliosis and microinfarcts[76]. The condition involves the whole brain and increases the risk of stroke, as well as impairment[77]. Additional features may also include a decreased number of lenticulostriate arteries[78], lacunar infarcts and dilated Virchow-Robin (perivascular CSF) spaces[79] (table 2). CSVD is commonly quantified according to the Fazekas Scale[80,81] (fig 3). Its severity has been found to be a strong predictor of functional cognitive decline and linked to morbidity and mortality of those suffering from it in numerous cohorts of several European Centres. These subjects may improve when all the underlying cardiovascular risk factors are well controlled[82].

Table 2: descriptors, imaging modality & quantification of chronic hypertensive encephalopathy

Chronic Hypertensive Encephalopathy Findings on Imaging			
Feature	**Imaging type**	**Finding**	**Quantification**
White matter changes	CT	Hypodensities	Fazekas scale
	MR: T2/FLAIR MR: T1	Hyperintensities Hypointensities	Fazekas scale
Microbleeds	MR: SWI/T2*	Punctate/linear dark foci	Boston criteria
Lacunar infarcts	MR: all sequences	Encephalomalacia foci	Number
Dilated VR spaces	CT or MR	CSF filled punctate or linear foci	Type, number
Atrophy	CT/MR	Widened sulci	Cortical atrophy scale
Vascular deformity	CTA/MRA/DSA	Tortuosity, beaded contours, Coiling	Calibre, symmetry, extension

CSVD appear as hyperintense (bright) areas on T2 and FLAIR MRI sequences [83]. They may also appear as hypointense (dark) areas on T1, also dark (hypodense) on CT, with a decreased diffusivity on diffusion tractography (DTI) and decreased perfusion in the subcortical white matter[84].

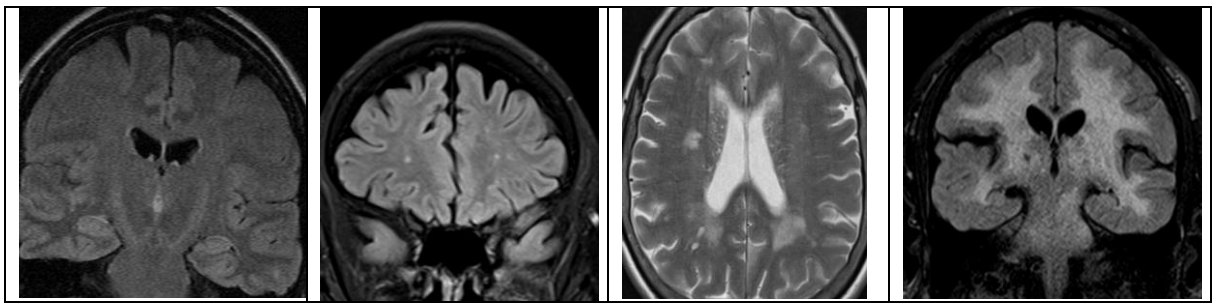


Figure 5: Comparison of a normal scan (first on the left) to punctate white matter hyperintensities for Fazekas 1/3 (second from the left), early confluence of white matter changes for Fazekas 2/3 (third from the left), and extensive and confluent white matter hyperintensities for Fazekas 3/3, on the right.

Initially appearing as few scattered punctate foci of white matter T2 hyperintensities not attenuating on sequences with free fluid attenuation (FLAIR), they become patchy bright T2 foci in the posterior circulation territory and vascular border zone [85] when they aggravate to then turn into extensive confluence in advanced stages of the disease [86] (fig 5).

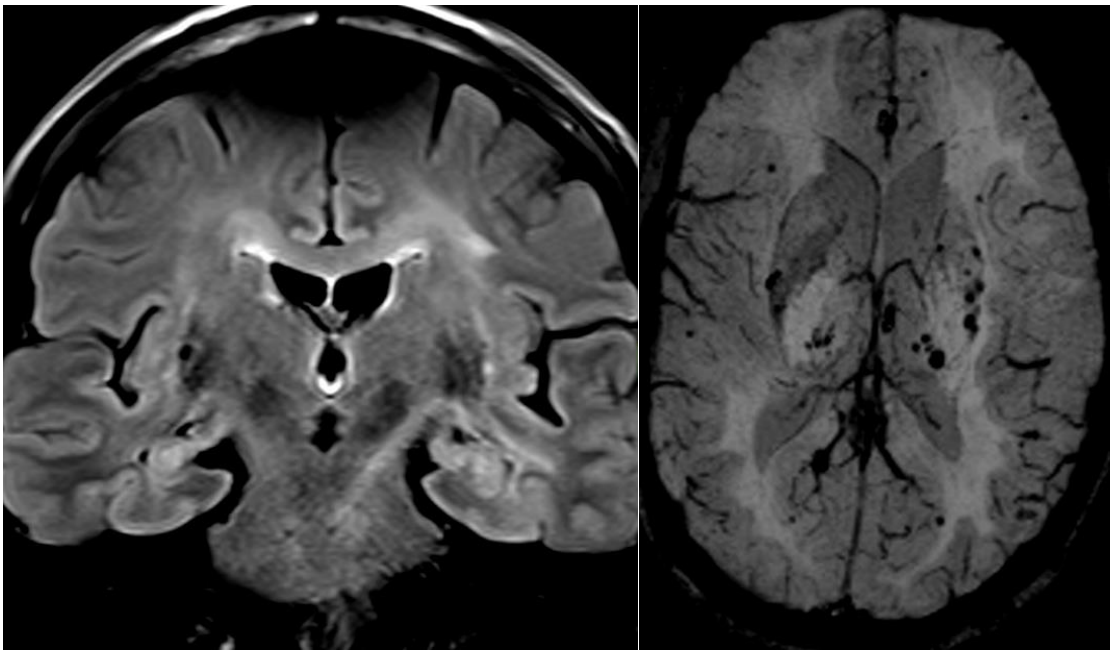


Figure 6: typical findings in chronic hypertensive encephalopathy including extensive cerebral small vessel disease (Fazekas 3/3) and chronic microbleeds with a characteristic pattern, predominantly affecting basal ganglia, brainstem, thalami and cerebellum over cerebral lobes. There is an underlying degree of Wallerian degeneration in the left corticospinal tract at rostral cerebral peduncle secondary to a previous ischaemic lesion in the left frontal lobe.

Cerebral microbleeds, another biomarker of CSVD in HTN, are small deposits of blood subproducts, predominantly haemosiderin, identified as black dots on MRI, particularly on T2* pulse sequences, corresponding to residues from previous episodes of bleeding and frequently related to foci of small vessel disease [87, 88]. MRI pulse sequences particularly sensitive to detect them are called susceptibility-weighted images, sensitivity which increases in direct proportion to the magnetic field strength[89] of the MR unit in which the patient is assessed (Fig 7).

As a marker of haemorrhage-prone small vessel disease, microbleeds require counting them to quantify their burden as 1, 2-4, ≥5, >10 and establishing their pattern of distribution i.e.: lobar, non-lobar or mixed [90]. The former is associated with cerebral amyloid angiopathy, quantifiable by the Boston Criteria, [91] later extended to other patterns as in chronic hypertensive encephalopathy[55, 56](figs 5 and 7).

Conditions to which cerebral microbleeds are associated include ageing, cerebral amyloid angiopathy (Fig 6), Alzheimer's Disease, cerebrovascular disease, chronic hypertensive encephalopathy (Fig 7), diffuse axonal injury[92], septic emboli[93] melanoma metastases[94], multiple familiar cerebral cavernomas [95], cardiothoracic surgery with extracorporeal circulation [96] and cerebral radiation therapy[97]; much less frequently but still possible, metastasis from sarcomas may present acutely as macro or microbleeds [98,99](fig 8).

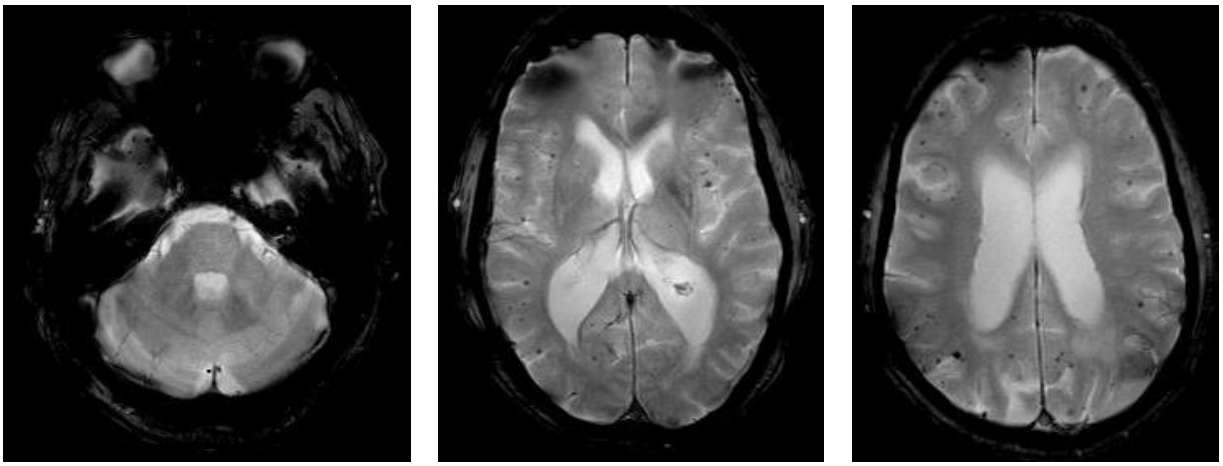


Figure 7: microbleeds with a cerebral amyloid angiopathy pattern, cortical and distributes in the cerebral lobes

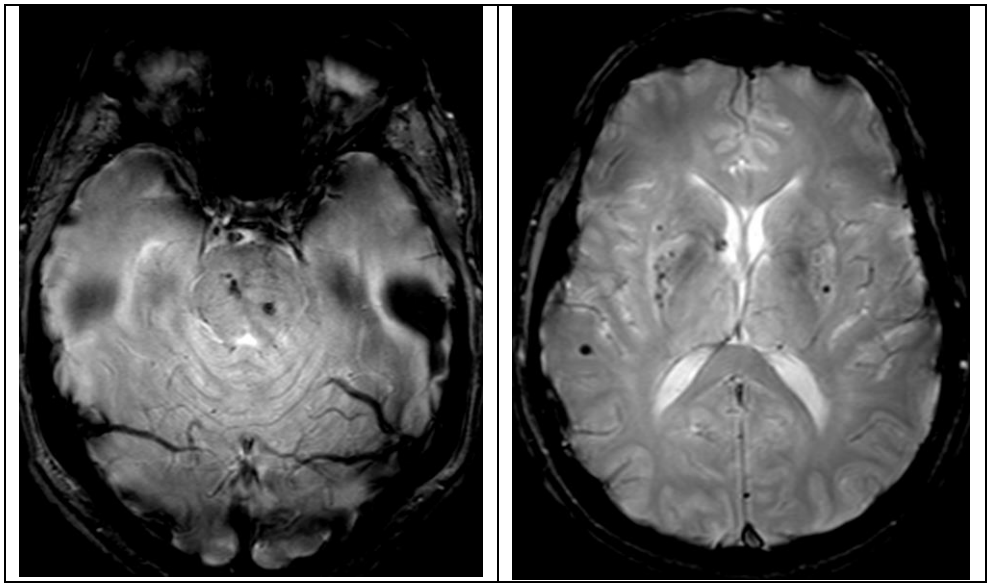
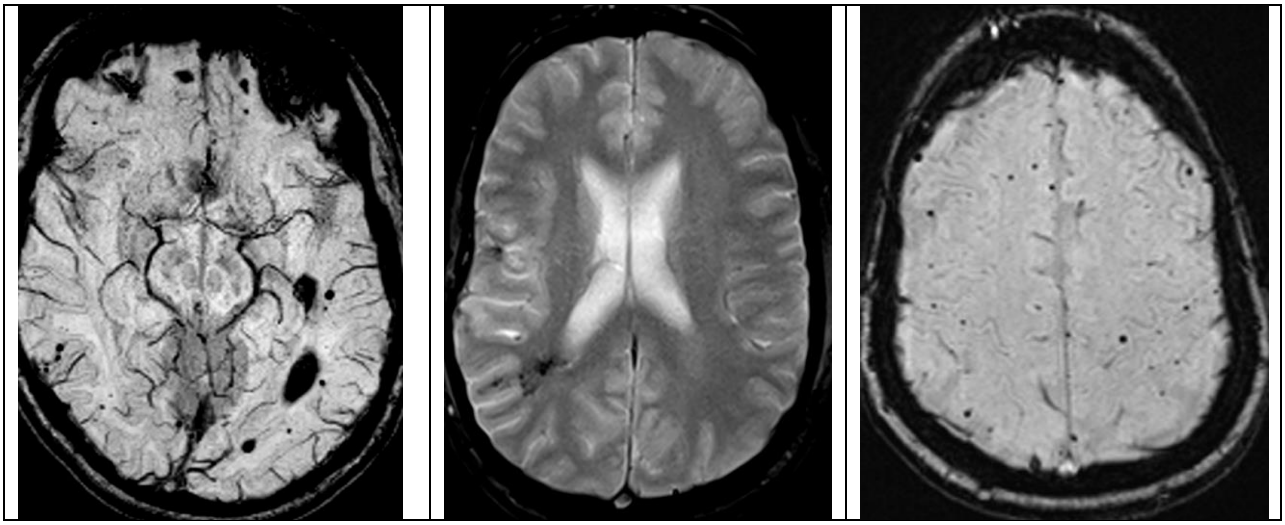


Figure 8: microbleeds with a chronic hypertensive encephalopathy pattern, distributed in basal ganglia and brainstem



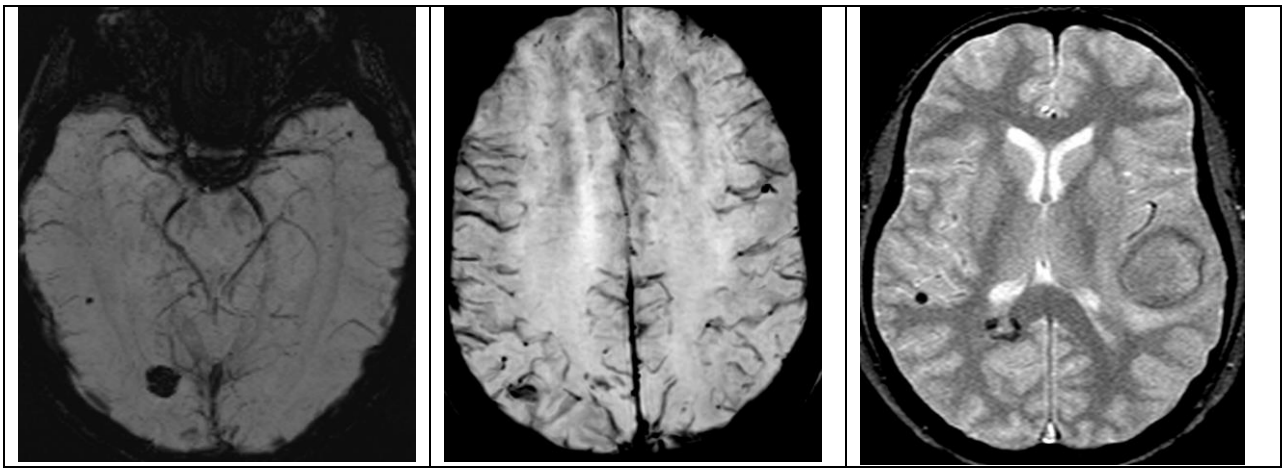


Figure 9: differential diagnoses of bleeds and microbleeds include several conditions; Cavernomas (venous angiomas) may present as a single or a myriad of foci, the latter in cases of familiar cerebral cavernomas as shown on top left image in a 28-year-old female. Top middle corresponds to actinic microbleeds in a 47-year-old male 2 years after radiotherapy for WHO 3 glioblastoma. Top right is a 22-year-old female with microbleeds secondary to extracorporeal circulation for cardiovascular surgery as a young adolescent. Melanoma metastases are shown on bottom left, septic bleeds are seen in a 48-year-old female on bottom middle and metastasis from an angiosarcoma are shown in bottom right on a 22-year-old male presented with seizures.

The most frequent cause of cerebral microbleeds with a non-lobar or mixed pattern in common practice tends to be HTN[100], which also developed in animal models subject to a high salt diet[101], being related to a higher incidence of spontaneous intra cerebral bleeds, worse outcomes in acute cerebrovascular disease and higher incidence of post thrombolysis bleeds[57].

The third biomarker of HTN CSVD are lacunae, named coined 200 years ago to define infarctions caused by small vessels[102], later characterized in post-mortem histopathological studies of lacunar stroke, subsequently correlated by neuroimaging studies (fig 9) for detection and quantification and were of paramount importance in defining Cerebral Small Vessel Disease[53,103], classified by Miller-Fisher in five main syndromic groups [67,104], among which, the lacunar syndromes may be considered predictors of lacunar and non-lacunar infarcts on neuroimaging, particularly in cases of atrial fibrillation[105].

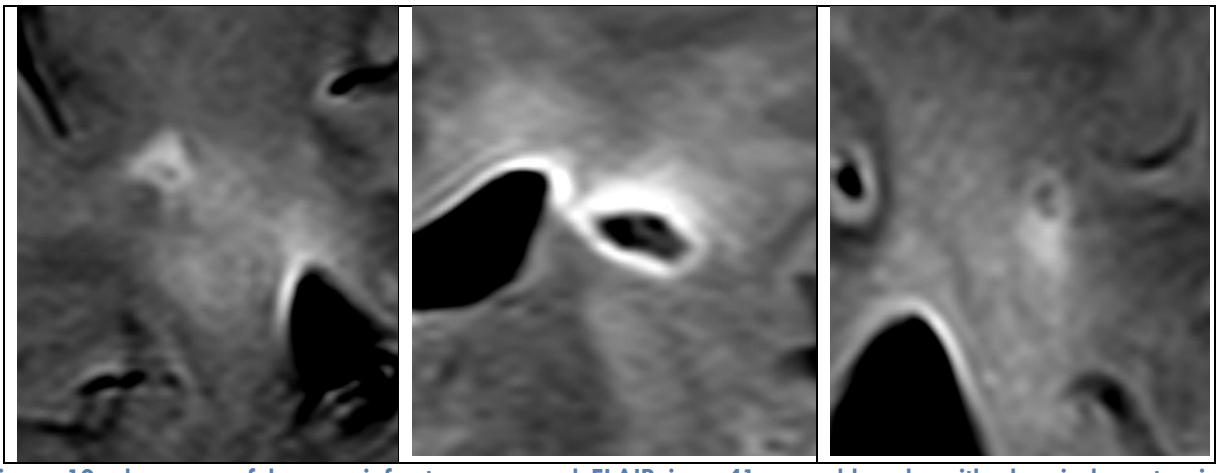


Figure 10: close ups of lacunar infarcts on coronal FLAIR in a 41-year-old male with chronic hypertensive encephalopathy since his mid twenties

An additional biomarker of HTN-related CSVD is dilated, prominent and numerous Virchow-Robin spaces (VRS)[106,107] (Fig 10). VRS are perivascular with CSF flowing through, driven by arterial pulsatility[108]. They form part of the glymphatic system of the brain, a waste metabolite drainage system consisting of CSF surrounding penetrating arteries to then disperse into the interstitial fluid via acquaporin-4 water channels. These waste metabolites flow out via large calibre veins to then

exit the brain via meningeal lymphatic vessels or venous sinuses [109]. It can be non-invasively evaluated [110] following Taoka's method which introduced the analysis along the perivascular space (ALPS) [111], followed by Kikuta et al to investigate diffusivity changes in elderly subjects with HTN[112], finding decreased ALPS indexes in hypertensive compared to control participants. Impaired glymphatic transport was also found on models of spontaneously hypertensive animals [113] Additional studies found dilated perivascular spaces and degenerative myelin changes in subjects with extensive small vessel disease and an association between arterial stiffness and myelin damage in the white matter[114,115].

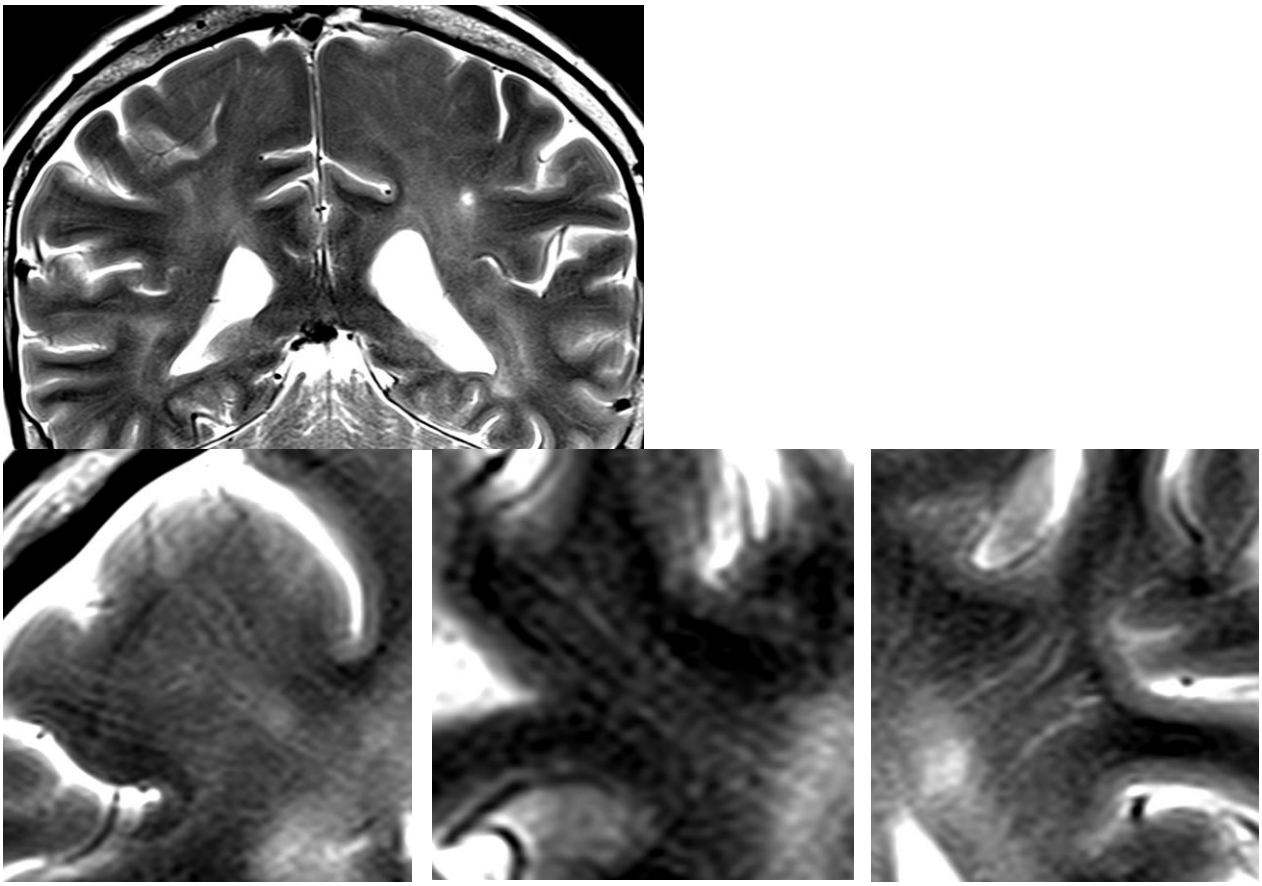


Figure 11: generalised prominence of Virchow-Robin spaces (white lines) in a 41-year-old male with chronic hypertensive encephalopathy on a coronal T2 (top) and close ups of the right mid frontal gyrus (bottom left), right inferior parietal gyrus (bottom middle) and left inferior parietal gyrus (bottom right)

Atrophy changes in the brain are an additional feature of HTN-related CSVD[79, 14](Fig 12). It tends to have a diffuse and non-specific pattern better identifiable by evaluating the structural relationship between the volumes of both, grey and white matter [116] on automated segmentation techniques[117], and diffusion tractography imaging in association commissural and limbic tracts [118] being associated to hippocampal atrophy rates overlapping to some extent with Alzheimer's Disease [119, 120, 121], posing challenges in the differential diagnosis among both on nuclear medicine studies[122].

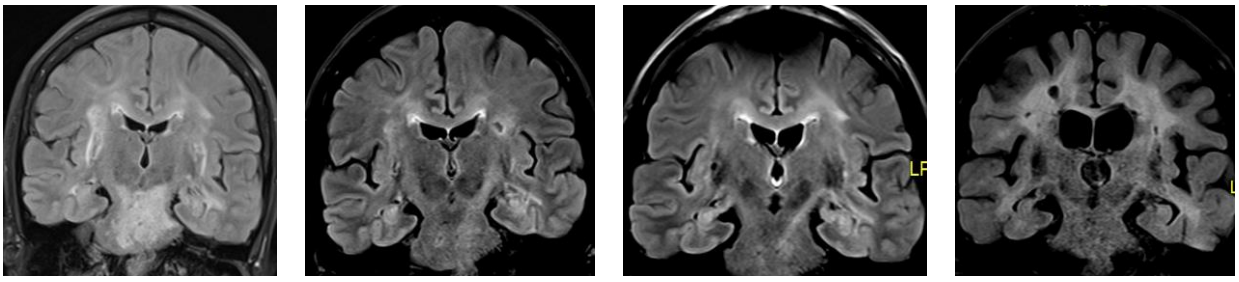


Figure 12: Progressive cortical atrophy in chronic hypertensive encephalopathy. 12a: acute on chronic hypertensive encephalopathy in a 41-year-old male. 12b: follow up scan in 8 months. 12c: follow up scan 2 years later. 12d: 8 years after the initial scan, when there was significant cognitive deterioration at age 49.

The most frequent vascular arterial changes seen in hypertensive subjects with cerebrovascular disease in current neuroimaging include wall thickening, vascular deformities, focal and/or diffuse stenosis and dissection.

HTN causes mechanical vessel wall injury in both micro and macro circulatory systems leading to endothelial dysfunction, subsequent impairment in mechanisms of endothelial-mediated vasodilatation and fibrinolysis [123], and vascular remodelling, term applied to changes in the smooth muscle cells of the vessel wall[124]. The latter, key in determining the vessel diameter, plays a paramount influence in determining blood pressure which results from multiplying the cardiac output by the total peripheral vascular resistance[125,126]. The earliest indicators of the disease can be identified on carotid Doppler by measuring intima-media thickness (cIMT) and assessing the pulse wave velocity, both already increased in pre HTN states [127] and markers of subclinical organ damage[128].

Dolichoarteriopathy is a term includes large and mid arterial kinking, coiling (loop or spiral shape) and tortuosity[129] (fig 11), as the spectra of HTN-related vasculopathy, an independent predictor of arterial wall thickness [130], leading risk factor causing carotid stenosis[131], presence of CSVD and acute ischaemic stroke[132,133].

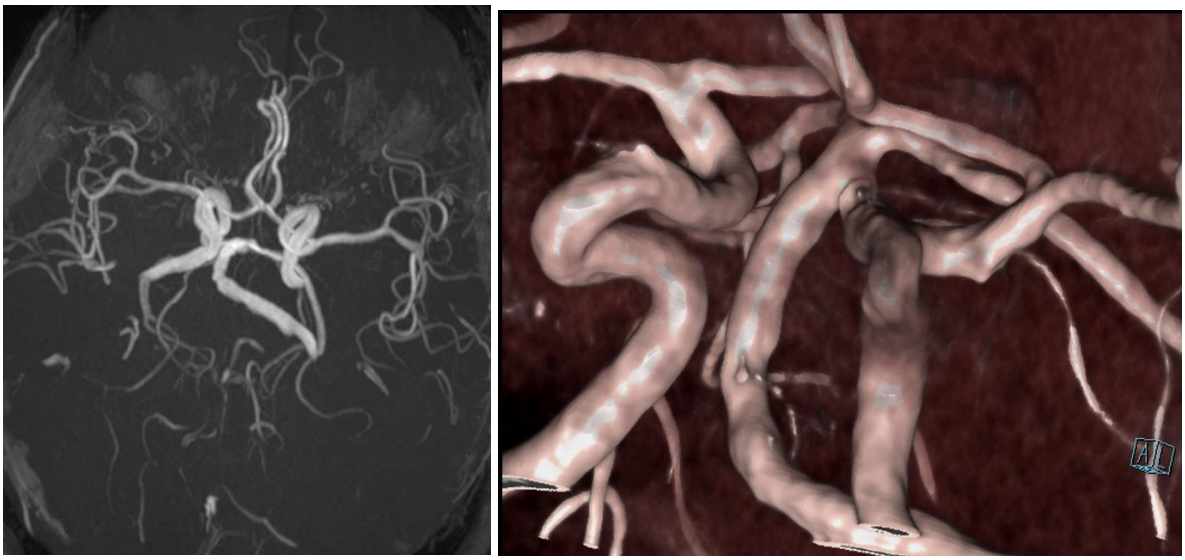


Figure 13: marked dolichoectasia of the basilar artery in a 45-year-old longstanding hypertensive male shown on multiple intensity projection (MIP) on the left and on 3D reformats on the right.

Conclusion

HTN changes in the brain may appear in different clinical presentations (fig 14), which also may, in time, appear alternatively in the same patient (figs 12 & 14), particularly in those non-compliant with prescribed treatments and requiring frequent admissions when acute crises become frankly symptomatic.

Our data suggests clinical referrals in our Institution tend to underestimate HTN when providing clinical information to justify exams requested in subject with symptoms of stroke, TIA

or acute cognitive deterioration, by not mentioning it when it should always be made explicit in order to facilitate the radiologists' process of vetting adequate imaging protocols and interpretation of findings. Radiologists should in our Institution describe and quantify neuroimaging findings attributable to HTN, particularly where they concern areas of restricted diffusion, the presence and extension of small vessel disease, microinfarcts, microbleeds, atrophy and signs of dolicoarteriopathy, not only in acute patients but also in those referred for cognitive deficits, given the impact dementia has in current clinical practise. Most importantly, hypertensive encephalopathy patients should be discussed at relevant multidisciplinary meetings to ensure adequate clinical and radiological input, facilitate diagnosis, therapeutic approach and follow up when clinically necessary, to minimise risk and avoid or delay incidence of devastating clinical consequences HTN, also known as the "silent killer", causes in the central nervous system.

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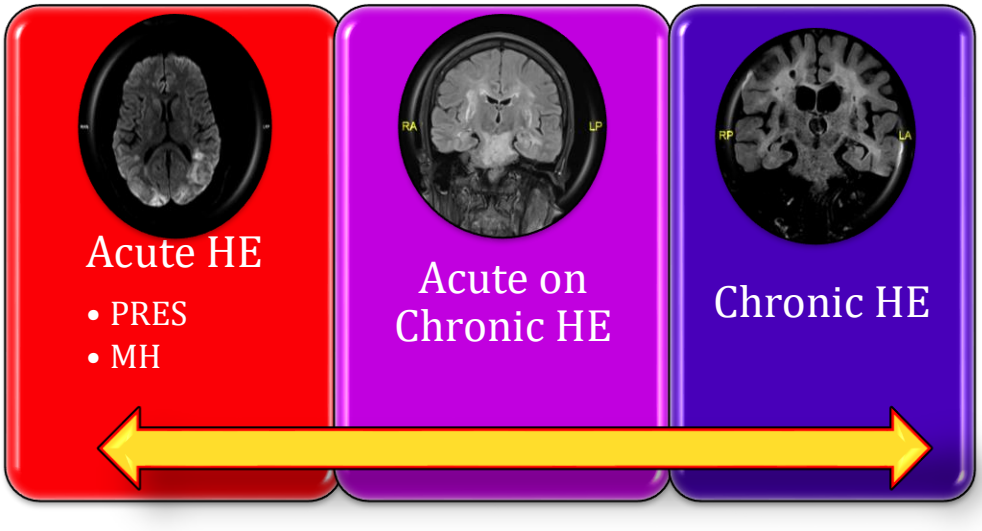

Figure 14: Different presentations of Hypertensive Encephalopathy which may bee seen in the same subject throughout the months or years

References

[1] Ezzati M, Zhou B, Carrillo-Larco R, Danaei G, Riley L, Paciorek R et al: Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. 2021 *The Lancet* 398 (10304): 957-980.

[2] Tu N Nguyen, Clara K Chow: Global and national high blood pressure burden and control, *The Lancet* 2021; 398(10304), 923-933. ISSN 0140-6736, doi.org/10.1016/S0140-6736(21)01688-3.

[3] Nadar, S. and G. Y. H. Lip (2009). *Hypertension*. Oxford, Oxford University Press.

[4] Mills, K.T., Stefanescu, A. & He, J. The global epidemiology of hypertension. *Nat Rev Nephrol* **16**, 223–237 (2020). doi.org/10.1038/s41581-019-0244-2

[5] Global burden of disease risk factors collaborators. Global, regional and national comparatrive risk assessment of 84 behavioural, environmental and occupational , and metabolic rosks or clusters of risks for the Global Burden of Disease Study 2017. *Lancet* 2018;392:1923-1994. doi.org/10.1016/S0140-6736(18)32225-6

[6] Pathak A, Kumar P, Pandit A, K, Chakravarty K, Misra S, Yadav A, K, Prasad K: Is Prevalence of Hypertension Increasing in First-Ever Stroke Patients?: A Hospital-Based Cross-Sectional Study. *Ann Neurosci* 2018;25:219-222. doi: 10.1159/000487066

[7] Donkor ES. Stroke in the 21st Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. *Stroke Res Treat*. 2018 Nov 27;2018:3238165. doi: 10.1155/2018/3238165. PMID: 30598741; PMCID: PMC6288566.

[8] Lopez AD, Mahers CD, Ezzati M, Jamison DT, Murray CJ: Global and regional burden of disease and risk factors, 2001: Systematic Analysis of Population Health Data. *Lancet* 2006;3671747-1757.

[9] Johnson W., Nguyen M.L., Patel R. Hypertension Crisis in the Emergency Department. *Cardiol. Clin.* 2012;30:533–543. doi: 10.1016/j.ccl.2012.07.011

[10] Tocci G., Sciarretta S., Volpe M. Development of heart failure in recent hypertension trials. *J. Hypertens.* 2008;26:1477–1486. doi: 10.1097/HJH.0b013e3282fe1d3d

[11] Balahura AM, Moroi ȘI, Scafa-Udriște A, Weiss E, Japie C, Bartoș D, Bădilă E. The Management of Hypertensive Emergencies-Is There a "Magical" Prescription for All? *J Clin Med*. 2022 May 31;11(11):3138. doi: 10.3390/jcm11113138. PMID: 35683521; PMCID: PMC9181665.

[12] Wenzel UO, Kemper C, Bode M. The role of complement in arterial hypertension and hypertensive end organ damage. *Br J Pharmacol*. 2021 Jul;178(14):2849-2862. doi: 10.1111/bph.15171. Epub 2020 Aug 19. PMID: 32585035.

[13] Gebremedhin D, Gopalakrishnan S, Harder DR. Endogenous events modulating myogenic regulation of cerebrovascular function. *Curr Vasc Pharmacol*. 2014;12(6):810-7. doi: 10.2174/15701611113116660153. PMID: 24066934.

[14] Cipolla M: *The Cerebral Circulation*, Morgan & Claypool Life Sciences, 2010, PMID 21452434

[15] Cipolla MJ, Liebeskind DS, Chan SL. The importance of comorbidities in ischemic stroke: Impact of hypertension on the cerebral circulation. *J Cereb Blood Flow Metab*. 2018 Dec;38(12):2129-2149. doi: 10.1177/0271678X18800589. Epub 2018 Sep 10. PMID: 30198826; PMCID: PMC6282213.

[16] Strandgaard S, Olesen J, Skinhoj E, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. *Br Med J*. 1973 Mar 3;1(5852):507-10. doi: 10.1136/bmj.1.5852.507. PMID: 4692673; PMCID: PMC1588676.

[17] Barry DI, Strandgaard S, Graham DI, Braendstrup O, Svendsen UG, Vorstrup S, Hemmingsen R, Bolwig TG. Cerebral blood flow in rats with renal and spontaneous hypertension: resetting of the lower limit of autoregulation. *J Cereb Blood Flow Metab*. 1982 Sep;2(3):347-53. doi: 10.1038/jcbfm.1982.35. PMID: 7096459.

[19] Hossmann KA. Viability thresholds and the penumbra of focal ischemia. *Ann Neurol*. 1994 Oct;36(4):557-65. doi: 10.1002/ana.410360404. PMID: 7944288.

[20] Rennels M, Nelson E. Capillary innervation in the mammalian central nervous system: an electron microscope demonstration (1). *Am J Anat*. 1975; 144: pp. 233–241

[21] Cipolla MJ, Li Rui, Vitullo L. Perivascular innervation of penetrating brain parenchymal arterioles. *J Cardiovasc Pharm*. 2004; 44(1): pp. 1–8.10.1097/00005344-200407000-00001

[22] Nishimura N, Schaffer CB, Friedman B, Lyden PD, Kleinfeld D. Penetrating arterioles are the bottleneck in the perfusion of neocortex. *Proc Natl Acad Sci USA*. 2007; 104: pp. 365–370.10.1073/pnas.0609551104

[23] Wei L, Otsuka T, Acuff V, Bereczki D, Pettigrew K, Patlak C, Fenstermacher J. The velocities of red cell and plasma flows through parenchymal microvessels of rat brain are decreased by pentobarbital. *J Cereb Blood Flow Metab*. 1993; 13: pp. 487–497

[24] Jacob M, Chappell D, Becker BF. Regulation of blood flow and volume exchange across the microcirculation. *Crit Care*. 2016 Oct 21;20(1):319. doi: 10.1186/s13054-016-1485-0. PMID: 27765054; PMCID: PMC5073467.

[25] Sokolova IA, Manukhina EB, Blinkov SM, Koshelev VB, Pinelis VG, Rodionov IM. Rare-faction of the arterioles and capillary network in the brain of rats with different forms of hypertension. *Microvasc Res*. 1985; 30: pp. 1–9.

[26] Punyaratabandhu N, Dechadilok P, Triampo W, Katavetin P. Hydrodynamic Model for Renal Microvascular Filtration: Effects of Physiological and Hemodynamic Changes on Glomerular Size-selectivity. *Microcirculation*. 2022 Jul 25:e12779. doi: 10.1111/micc.12779. Epub ahead of print. PMID: 35879876.

[27] Sokolova IA, Manukhina EB, Blinkov SM, Koshelev VB, Pinelis VG, Rodionov IM. Rarefication of the arterioles and capillary network in the brain of rats with different forms of hypertension. *Microvasc Res*. 1985 Jul;30(1):1-9. doi: 10.1016/0026-2862(85)90032-9. PMID: 4021832.

[28] Feihl F, Liaudet L, Waeber B. The macrocirculation and microcirculation of hypertension. *Curr Hypertens Rep*. 2009 Jun;11(3):182-9. doi: 10.1007/s11906-009-0033-6. PMID: 19442327.

[29] Pires PW, Dams Ramos CM, Matin N, Dorrance AM. The effects of hypertension on the cerebral circulation. *Am J Physiol Heart Circ Physiol*. 2013 Jun 15;304(12):H1598-614. doi: 10.1152/ajpheart.00490.2012. Epub 2013 Apr 12. PMID: 23585139; PMCID: PMC4280158.

[30] Cipolla MJ, Liebeskind DS, Chan SL. The importance of comorbidities in ischemic stroke: Impact of hypertension on the cerebral circulation. *J Cereb Blood Flow Metab*. 2018 Dec;38(12):2129-2149. doi: 10.1177/0271678X18800589. Epub 2018 Sep 10. PMID: 30198826; PMCID: PMC6282213.

[31] van der Veen PH, Geerlings MI, Visseren FL, et al. Hypertensive Target Organ Damage and Longitudinal Changes in Brain Structure and Function: The Second Manifestations of Arterial Disease-Magnetic Resonance Study. *Hypertension*. 2015;66(6):1152-1158. doi:10.1161/HYPERTENSIONAHA.115.06268

[32] Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol*. 2005;4(8):487-499. doi:10.1016/S1474-4422(05)70141-1

[33] Ungvari, Z., Toth, P., Tarantini, S. *et al*. Hypertension-induced cognitive impairment: from pathophysiology to public health. *Nat Rev Nephrol* **17**, 639–654 (2021). doi.org/10.1038/s41581-021-00430-6

[34] Sinnott SJ, Smeeth L, Williamson E, Douglas IJ. Trends for prevalence and incidence of resistant hypertension: population based cohort study in the UK 1995-2015. *BMJ*. 2017 Sep 22;358:j3984. doi: 10.1136/bmj.j3984. PMID: 28939590; PMCID: PMC5609092.

[35] Ogata J, Yamanishi H, Ishibashi0Hueda H: Chapter 2: Pathology of cerebral small vessel disease, in Pantoni L, Gorelick P: *Cerebral small vessel disease*. Cambridge University Press, 2014: 4-15.

[36] Khan U, Porteous L, Hassan A, Markus HS. Risk factor profile of cerebral small vessel disease and its subtypes. *J Neurol Neurosurg Psychiatry*. 2007;78(7):702-706. doi:10.1136/jnnp.2006.103549

[37] Hilal S, Mok V, Youn YC, Wong A, Ikram MK, Chen CL. Prevalence, risk factors and consequences of cerebral small vessel diseases: data from three Asian countries. *J Neurol Neurosurg Psychiatry*. 2017 Aug;88(8):669-674. doi: 10.1136/jnnp-2016-315324. Epub 2017 Jun 9. PMID: 28600443.

[38] Liu Y, Dong YH, Lyu PY, Chen WH, Li R. Hypertension-Induced Cerebral Small Vessel Disease Leading to Cognitive Impairment. *Chin Med J* (Engl). 2018 Mar 5;131(5):615-619. doi: 10.4103/0366-6999.226069. PMID: 29483399; PMCID: PMC585068

[39] Quick S, Moss J, Rajani RM, Williams A. A Vessel for Change: Endothelial Dysfunction in Cerebral Small Vessel Disease. *Trends Neurosci*. 2021 Apr;44(4):289-305. doi: 10.1016/j.tins.2020.11.003. Epub 2020 Dec 8. PMID: 33308877.

[40] Pantoni L. Chapeter 1: Definition and classification of small vessel diseases, in Pantoni L, Gorelick P: *Cerebral small vessel disease*, Cambridge University Press 2014:1-3.

[41] Biffi A, Greenberg SM. Cerebral amyloid angiopathy: a systematic review. *J Clin Neurol* 2011;7:1-9.

[42] Schmidt R, Cavalieri M, Loitfelder M: Chapter 27: Cerebral small vessel disease imaging as a surrogate marker for clinical trials. In Pantoni L, Gorelick P: *Cerebral small vessel disease*, Cambridge University Press. 2014:336-346.

[43] Fazekas F, Niederkorn K, Schmidt R, Offenbacher H, Horner S, Bertha G et al. White matter signal abnormalities in normal individuals: correlation with carotid ultrasonography, cerebral blood flow measurements, and cerebrovascular risk factors. *Stroke*. 1988;19(10):1285-1288. doi:10.1161/01.str.19.10.1285

[44] de Leeuw FE, de Groot JC, Oudkerk M, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain*. 2002;125(Pt 4):765-772. doi:10.1093/brain/awf077

[45] Jeerakathil T, Wolf PA, Beiser A, et al. Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. *Stroke*. 2004;35(8):1857-1861. doi:10.1161/01.STR.0000135226.53499.85

[46] Poels MM, Vernooij MW, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. *Stroke*. 2010;41(10 Suppl):S103-S106. doi:10.1161/STROKEAHA.110.595181

[47] van Ommen F, Dankbaar JW, Zhu G, Wolman DN, Heit JJ, Kauw F, et al: Virtual monochromatic dual-energy CT reconstructions improve detection of cerebral infarct in patients with suspicion of stroke. *Neuroradiology*. 2021 Jan;63(1):41-49. doi: 10.1007/s00234-020-02492-y. Epub 2020 Jul 29. PMID: 32728777; PMCID: PMC7803871.

[48] Standards for radiology events and learning meetings. The Royal College of Radiology, January 2020, accessed on 1st February 2022, https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfcr201-standards-for-radiology-events-and-learning-meetings.pdf

[49] Price RS, Kasner SE. Hypertension and hypertensive encephalopathy. *Handb Clin Neurol*. 2014;119:161-7. doi: 10.1016/B978-0-7020-4086-3.00012-6. PMID: 24365295.

[50] Papadopoulos DP, Mourouzis I, Thomopoulos C, Makris T, Papademetriou V. Hypertension crisis. *Blood Press*. 2010 Dec;19(6):328-36. doi: 10.3109/08037051.2010.488052. Epub 2010 May 27. PMID: 20504242.

[51] Osborn A: Acquired Metabolic and Systemic Disorders, Chapter 32, pp1017-29, in Osborn A: *Osborn's Brain*, 2018 Elsevier, ISBN 978-0-323-4776-5

[52] Okamoto K, Motohashi K, Fujiwara H, Ishihara T, Ninomiya I, Onodera O, Fujii Y. [PRES: Posterior Reversible Encephalopathy Syndrome]. *Brain Nerve*. 2017 Feb;69(2):129-141. Japanese. doi: 10.11477/mf.1416200653. PMID: 28202821.

[53] Parasher A, Jhamb R. Posterior reversible encephalopathy syndrome (PRES): presentation, diagnosis and treatment. *Postgrad Med J*. 2020 Oct;96(1140):623-628. doi: 10.1136/postgradmedj-2020-137706. Epub 2020 May 28. PMID: 32467104.

[54] Barber E, Nugzar R, Finkelshtein V, Puzhevsky A, Levy T. Posterior reversible encephalopathy syndrome case report in an untreated, normotensive, ovarian cancer patient in the presence of paraneoplastic antibodies. *BMC Neurol*. 2020 Sep 2;20(1):330. doi: 10.1186/s12883-020-01913-y. PMID: 32878599; PMCID: PMC7466806.

[55] O'Kane M, Elhalwagy H, Kumar S, Badawi C. Unusual presentation of PRES in the postnatal period. *BMJ Case Rep*. 2014 Jul 9;2014:bcr2013203406. doi: 10.1136/bcr-2013-203406. PMID: 25008333; PMCID: PMC4091404.

[56] Aduen-Carrillo A, Hernandez-Woodbine MJ, Avendaño-Capriles CA, Ayola-Anaya FN. Initial Normotensive Presentation of a Primigravida With Posterior Reversible Encephalopathy Syndrome: A Case Report. *Cureus*. 2021 Nov 9;13(11):e19407. doi: 10.7759/cureus.19407. PMID: 34909327; PMCID: PMC8658731.

[57] Hugonnet E, Da Ines D, Boby H, Claise B, Petitcolin V, Lannarei et al. Posterior reversible encephalopathy syndrome (PRES): features on CT and MR imaging. *Diagn Interv Imaging*. 2013 Jan;94(1):45-52. doi: 10.1016/j.diii.2012.02.005. Epub 2012 Jul 24. PMID: 22835573.

[58] Rodrigues SG, Saraiva P, Marques IB. Optic pathways and brainstem involvement in posterior reversible encephalopathy syndrome. *BMJ Case Rep*. 2021 Jan 11;14(1):e239130. doi: 10.1136/bcr-2020-239130. PMID: 33431522; PMCID: PMC7802660.

[59] Honda K, Hashimoto S. Brainstem Cerebellum-type Posterior Reversible Encephalopathy Syndrome. *Intern Med*. 2020 May 15;59(10):1337-1338. doi: 10.2169/internalmedicine.3603-19. Epub 2020 Feb 12. PMID: 32051377; PMCID: PMC7303442.

[60] Cheng X, Li J Lan Y, Liu J, Chen S, Lu G. Cerebrovascular Disease in the Setting of Posterior Reversible Encephalopathy Syndrome. *Front Neurol*. 2021 Nov 17;12:765333. doi: 10.3389/fneur.2021.765333. PMID: 34867751; PMCID: PMC8635685.

[61] Astarita A, Covella M, Vallelonga F, Cesareo M, Totaro S, Ventre L, Aprà F et al. Hypertensive emergencies and urgencies in emergency departments: a systematic review and meta-analysis. *J Hypertens*. 2020 Jul;38(7):1203-1210. doi: 10.1097/HJH.0000000000002372. PMID: 32510905.

[62] Naranjo M, Chauhan S, Paul M. Malignant Hypertension. 2022 Apr 6. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 29939523.

[63] Lewek J, Bielecka-Dąbrowa A, Maciejewski M, Banach M. Pharmacological management of malignant hypertension. *Expert Opin Pharmacother*. 2020 Jul;21(10):1189-1192. doi: 10.1080/14656566.2020.1732923. Epub 2020 Feb 26. PMID: 32100590

[65] Polgreen LA, Suneja M, Tang F, Carter BL, Polgreen PM. Increasing trend in admissions for malignant hypertension and hypertensive encephalopathy in the United States. *Hypertension*. 2015 May;65(5):1002-7. doi: 10.1161/HYPERTENSIONAHA.115.05241. Epub 2015 Mar 23. PMID: 25801877.

[66] Kim ST, Park T. Acute and Chronic Effects of Cocaine on Cardiovascular Health. *Int J Mol Sci*. 2019 Jan 29;20(3):584. doi: 10.3390/ijms20030584. PMID: 30700023; PMCID: PMC6387265.

[67] Goel N, Pullman JM, Coco M. Cocaine and kidney injury: a kaleidoscope of pathology. *Clin Kidney J*. 2014 Dec;7(6):513-7. doi: 10.1093/ckj/sfu092. Epub 2014 Sep 12. PMID: 25859366; PMCID: PMC4389131.

[68] Guyenet PG, Stornetta RL, Souza GMPR, Abbott SBG, Brooks VL. Neuronal Networks in Hypertension: Recent Advances. *Hypertension*. 2020 Aug;76(2):300-311. doi: 10.1161/HYPERTENSIONAHA.120.14521. Epub 2020 Jun 29. PMID: 32594802; PMCID: PMC7347452.

[69] Lifson N, Pasquale A, Salloum G, Alpert S. Ophthalmic Manifestations of Posterior Reversible Encephalopathy Syndrome. *Neuroophthalmology*. 2018 Aug 17;43(3):180-184. doi: 10.1080/01658107.2018.1506938. PMID: 31312242; PMCID: PMC6619982.

[70] Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010 Jul;9(7):689-701. doi: 10.1016/S1474-4422(10)70104-6. PMID: 20610345.

[71] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013 Aug;12(8):822-38. doi: 10.1016/S1474-4422(13)70124-8. PMID: 23867200; PMCID: PMC3714437.

[72] Brown R, Benveniste H, Black SE, Charpak S, Dichgans M, Joutel A et al. Understanding the role of the perivascular space in cerebral small vessel disease. *Cardiovasc Res*. 2018 Sep 1;114(11):1462-1473. doi: 10.1093/cvr/cvy113. PMID: 29726891; PMCID: PMC6455920.

[73] Litak J, Mazurek M, Kulesza B, Szmygin P, Litak J, Kamieniak P, Grochowski C. Cerebral Small Vessel Disease. *Int J Mol Sci*. 2020 Dec 20;21(24):9729. doi: 10.3390/ijms21249729. PMID: 33419271; PMCID: PMC7766314.

[74] Liu Y, Dong YH, Lyu PY, Chen WH, Li R. Hypertension-Induced Cerebral Small Vessel Disease Leading to Cognitive Impairment. *Chin Med J* (Engl). 2018 Mar 5;131(5):615-619. doi: 10.4103/0366-6999.226069. PMID: 29483399; PMCID: PMC5850681.

[75] Gychka, S.G., Shults, N.V., Sariipek, N.E., Rybka, V., Malysheva, T., Dibrova, V.A et al. Histological Characterizations of the Brain Vascular Hyalinosis in Patients with Systemic Hypertension-Induced Ischemic Stroke. *The FASEB Journal*, 34:1-1. doi.org/10.1096/fasebj.2020.34.s1.01801

[76] Bagi Z, Brandner DD, Le P, McNeal DW, Gong X, Dou H et al. Vasodilator dysfunction and oligodendrocyte dysmaturation in aging white matter. *Ann Neurol*. 2018 Jan;83(1):142-152. doi: 10.1002/ana.25129. PMID: 29283444; PMCID: PMC5876126.

[77] Shi Y, Wardlaw JM. Update on cerebral small vessel disease: a dynamic whole-brain disease. *Stroke Vasc Neurol*. 2016 Oct 25;1(3):83-92. doi: 10.1136/svn-2016-000035. PMID: 28959468; PMCID: PMC5435198.

[78] Chen YC, Li YH, Lu J, Li WB, Wang JB. Correlation Between the Reduction in Lenticulostriate Arteries Caused by Hypertension and Changes in Brain Metabolism Detected With MRI. *AJR Am J Roentgenol*. 2016 Feb;206(2):395-400. doi: 10.2214/AJR.15.14514. PMID: 26797370.

[79] Liu Y, Dong YH, Lyu PY, Chen WH, Li R. Hypertension-Induced Cerebral Small Vessel Disease Leading to Cognitive Impairment. *Chin Med J* (Engl). 2018 Mar 5;131(5):615-619. doi: 10.4103/0366-6999.226069. PMID: 29483399; PMCID: PMC5850681.

[80] Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, Wallin A. European Task Force on Age-Related White Matter Changes. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001 Jun;32(6):1318-22. doi: 10.1161/01.str.32.6.1318. PMID: 11387493.

[81] Iordanishvili E, Schall M, Loução R, Zimmermann M, Kotetishvili K, Shah NJ et al. Quantitative MRI of cerebral white matter hyperintensities: A new approach towards understanding the underlying pathology. *Neuroimage*. 2019 Nov 15;202:116077. doi: 10.1016/j.neuroimage.2019.116077. Epub 2019 Aug 6. PMID: 31398433.

[82] Inzitari D, Pracucci G, Poggesi A, Carlucci G, Barkhof F, Chabriat H et al. Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. *BMJ*. 2009 Jul 6;339:b2477. doi: 10.1136/bmj.b2477. PMID: 19581317; PMCID: PMC2714680.

[83] Iordanishvili E, Schall M, Loução R, Zimmermann M, Kotetishvili K, Shah NJ, Oros-Peusquens AM. Quantitative MRI of cerebral white matter hyperintensities: A new approach towards understanding the underlying pathology. *Neuroimage*. 2019 Nov 15;202:116077. doi: 10.1016/j.neuroimage.2019.116077. Epub 2019 Aug 6. PMID: 31398433.

[84] Huynh TJ, Murphy B, Pettersen JA, Tu H, Sahlas DJ, Zhang L et al. CT perfusion quantification of small-vessel ischemic severity. *AJNR Am J Neuroradiol*. 2008 Nov;29(10):1831-6. doi: 10.3174/ajnr.A1238. Epub 2008 Sep 3. PMID: 18768729; PMCID: PMC8118954.

[85] van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. *Stroke*. 2008 Oct;39(10):2712-9. doi: 10.1161/STROKEAHA.107.513176. Epub 2008 Jul 17. PMID: 18635849.

[86] Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF. CNS small vessel disease: A clinical review. *Neurology*. 2019 Jun 11;92(24):1146-1156. doi: 10.1212/WNL.0000000000007654. Epub 2019 May 29. PMID: 31142635; PMCID: PMC6598791.

[87] ALg VS, Werring D: Microaneurysms, cerebral microbleeds and intracerebral haemorrhage, in: *Cerebral Microbleeds*, Cambridge University Press 2011

[88] Linn J. Imaging of Cerebral Microbleeds. *Clin Neuroradiol*. 2015 Oct;25 Suppl 2:167-75. doi: 10.1007/s00062-015-0458-z. Epub 2015 Sep 4. PMID: 26337706.

[89] Haller S, Vernooij MW, Kuijer JPA, Larsson EM, Jäger HR, Barkhof F. Cerebral Microbleeds: Imaging and Clinical Significance. *Radiology*. 2018 Apr;287(1):11-28. doi: 10.1148/radiol.2018170803. PMID: 29558307.

[90] Charidimou A, Turc G, Oppenheim C, Yan S, Scheitz JF, Erdur H et al. Microbleeds, Cerebral Hemorrhage, and Functional Outcome After Stroke Thrombolysis. *Stroke*. 2017 Aug;48(8):2084-2090. doi: 10.1161/STROKEAHA.116.012992. PMID: 28720659.

[91] Charidimou A, Boulouis G, Frosch MP, Baron JC, Pasi M, Albucher JF, et al: The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol*. 2022 Aug;21(8):714-725. doi: 10.1016/S1474-4422(22)00208-3. PMID: 35841910; PMCID: PMC9389452.

[92] Scheid R, Preul C, Gruber O, Wiggins C, von Cramon DY. Diffuse axonal injury associated with chronic traumatic brain injury: evidence from T2*-weighted gradient-echo imaging at 3 T. *AJNR Am J Neuroradiol*. 2003;24:1049–56.

[93] Akel O, Raju B, Suresh SC, Jumah F, Gupta G, Nanda A. Multiple cerebral hemorrhages in sepsis-disseminated intravascular coagulation versus septic embolism: An image report. *Surg Neurol Int*. 2021 Apr 26;12:185. doi: 10.25259/SNI_810_2020. PMID: 34084613; PMCID: PMC8168679.

[94] Gaviani P, Mullins ME, Braga TA, Hedley-Whyte ET, Halpern EF, Schaefer PS et al. Improved detection of metastatic melanoma by T2*-weighted imaging. *AJNR Am J Neuroradiol*. 2006;27:605–8

[95] Sempere-Pérez A, Campistol J, García-Cazorla A, Guillén-Quesada A, Pérez-Muñoz N. Cavernomatosis múltiple cerebral familiar [Multiple familial cerebral cavernomatosis]. *Rev Neurol*. 2007 Jun 1-15;44(11):657-60. Spanish. PMID: 17557222.

[96] Patel N, Banahan C, Janus J, Horsfield MA, Cox A, Li X et al. Perioperative Cerebral Microbleeds After Adult Cardiac Surgery. *Stroke*. 2019 Feb;50(2):336-343. doi: 10.1161/STROKEAHA.118.023355. PMID: 30572811; PMCID: PMC6354910.

[97] Bian W, Hess CP, Chang SM, Nelson SJ, Lupo JM. Susceptibility-weighted MR imaging of radiation therapy-induced cerebral microbleeds in patients with glioma: a comparison between 3T and 7T. *Neuroradiology*. 2014 Feb;56(2):91-6. doi: 10.1007/s00234-013-1297-8. Epub 2013 Nov 27. PMID: 24281386; PMCID: PMC4940363.

[98] Takemori T, Kawamoto T, Morishita M, Hara H, Fukase N, Kawakami Y et al. Clinical Outcome of the Patients With Brain Metastasis from Soft Tissue Sarcomas. *Anticancer Res*. 2021 Feb;41(2):1027-1034. doi: 10.21873/anticanres.14858. PMID: 33517311.

[99] Chaigneau L, Patrikidou A, Ray-Coquard I, Valentin T, Linassier C, Bay JO et al. Brain Metastases from Adult Sarcoma: Prognostic Factors and Impact of Treatment. A Retrospective Analysis from the French Sarcoma Group (GSF/GETO). *Oncologist*. 2018 Aug;23(8):948-955. doi: 10.1634/theoncologist.2017-0136. Epub 2018 Jun 22. PMID: 29934413; PMCID: PMC6156185.

[100] Loewenstein D, Rabbat M. Neurological complications of systemic hypertension. *Handb Clin Neurol*. 2021;177:253-259. doi: 10.1016/B978-0-12-819814-8.00018-4. PMID: 33632444.

[101] Herisson F, Zhou I, Mawet J, Du E, Barfejani AH, Qin T et al. Posterior reversible encephalopathy syndrome in stroke-prone spontaneously hypertensive rats on high-salt diet. *J Cereb Blood Flow Metab*. 2019 Jul;39(7):1232-1246. doi: 10.1177/0271678X17752795. Epub 2018 Jan 19. PMID: 29350576; PMCID: PMC6668522.

[102] Regenhardt RW, Das AS, Ohtomo R, Lo EH, Ayata C, Gurol ME. Pathophysiology of Lacunar Stroke: History's Mysteries and Modern Interpretations. *J Stroke Cerebrovasc Dis*. 2019 Aug;28(8):2079-2097. doi: 10.1016/j.jstrokecerebrovasdis.2019.05.006. Epub 2019 May 28. PMID: 31151839; PMCID: PMC7416422.

[103] Fisher CM. Lacunar strokes and infarcts: a review. *Neurology*. 1982 Aug;32(8):871-6. doi: 10.1212/wnl.32.8.871. PMID: 7048128.

[104] Loeb C. The lacunar syndromes. *Eur Neurol*. 1989;29 Suppl 2:2-7. doi: 10.1159/000116454. PMID: 2693095.

[105] Giacomozzi S, Caso V, Agnelli G, Acciarresi M, Alberti A, Venti M et al. Lacunar stroke syndromes as predictors of lacunar and non-lacunar infarcts on neuroimaging: a hospital-based study. *Intern Emerg Med*. 2020 Apr;15(3):429-436. doi: 10.1007/s11739-019-02193-2. Epub 2019 Sep 18. PMID: 31535289.

[106] Chen X, Wang J, Shan Y, Cai W, Liu S, Hu M et al. Cerebral small vessel disease: neuroimaging markers and clinical implication. *J Neurol*. 2019 Oct;266(10):2347-2362. doi: 10.1007/s00415-018-9077-3. Epub 2018 Oct 5. PMID: 30291424.

[107] Wardlaw JM, Benveniste H, Nedergaard M, Zlokovic BV, Mestre H, Lee H, et al: Perivascular spaces in the brain: anatomy, physiology and pathology. *Nat Rev Neurol*. 2020 Mar;16(3):137-153. doi: 10.1038/s41582-020-0312-z. Epub 2020 Feb 24. PMID: 32094487.

[108] Mestre H, Tithof J, Du T, Song W, Peng W, Sweeney AM et al. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. *Nat Commun*. 2018 Nov 19;9(1):4878. doi: 10.1038/s41467-018-07318-3. PMID: 30451853; PMCID: PMC6242982.

[109] Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD et al. Structural and functional features of central nervous system lymphatic vessels. *Nature*. 2015 Jul 16;523(7560):337-41. doi: 10.1038/nature14432. Epub 2015 Jun 1. Erratum in: *Nature*. 2016 May 12;533(7602):278. PMID: 26030524; PMCID: PMC4506234.

[110] Taoka T, Naganawa S. Glymphatic imaging using MRI. *J Magn Reson Imaging*. 2020 Jan;51(1):11-24. doi: 10.1002/jmri.26892. Epub 2019 Aug 18. PMID: 31423710.

[111] Taoka T, Masutani Y, Kawai H, Nakane T, Matsuoka K, Yasuno F, Kishimoto T, Naganawa S. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. Jpn J Radiol. 2017 Apr;35(4):172-178. doi: 10.1007/s11604-017-0617-z. Epub 2017 Feb 14. PMID: 28197821

[112] Kikuta J, Kamagata K, Takabayashi K, Taoka T, Yokota H, Andica C et al. An Investigation of Water Diffusivity Changes along the Perivascular Space in Elderly Subjects with Hypertension. *AJNR Am J Neuroradiol*. 2022 Jan;43(1):48-55. doi: 10.3174/ajnr.A7334. Epub 2021 Nov 18. PMID: 34794943; PMCID: PMC8757561.

[113] Mortensen KN, Sanggaard S, Mestre H, Lee H, Kostrikov S, Xavier ALR et al. Impaired Glymphatic Transport in Spontaneously Hypertensive Rats. *J Neurosci*. 2019 Aug 7;39(32):6365-6377. doi: 10.1523/JNEUROSCI.1974-18.2019. Epub 2019 Jun 17. PMID: 31209176; PMCID: PMC6687896.

[114] Yamamoto Y, Ihara M, Tham C, et al. Neuropathological correlates of temporal pole white matter hyperintensities in CADASIL. *Stroke* 2009;40:2004–11

[115] Kamagata K, Andica C, Shimada K, et al. Effects of arterial stiffness on cerebral white matter integrity in the elderly. In: *Proceedings of the Annual Meeting of the International Society for Magnetic Resonance in Medicine and the Society for MR Radiographers & Technologists*, Virtual; August 8–14, 2020

[116] Kern KC, Wright CB, Bergfield KL, Fitzhugh MC, Chen K, Moeller JR et al. Blood Pressure Control in Aging Predicts Cerebral Atrophy Related to Small-Vessel White Matter Lesions. *Front Aging Neurosci*. 2017 May 15;9:132. doi: 10.3389/fnagi.2017.00132. PMID: 28555103; PMCID: PMC5430031.

[117] Frey BM, Petersen M, Mayer C, Schulz M, Cheng B, Thomalla G. Characterization of White Matter Hyperintensities in Large-Scale MRI-Studies. *Front Neurol*. 2019 Mar 26;10:238. doi: 10.3389/fneur.2019.00238. PMID: 30972001; PMCID: PMC6443932.

[118] de Groot M, Ikram MA, Akoudad S, Krestin GP, Hofman A, van der Lugt A et al. Tract-specific white matter degeneration in aging: the Rotterdam Study. *Alzheimers Dement*. 2015 Mar;11(3):321-30. doi: 10.1016/j.jalz.2014.06.011. Epub 2014 Sep 10. PMID: 25217294.

[119] Fiford CM, Nicholas JM, Biessels GJ, Lane CA, Cardoso MJ, Barnes J. High blood pressure predicts hippocampal atrophy rate in cognitively impaired elders. *Alzheimers Dement* (Amst). 2020 May 17;12(1):e12035. doi: 10.1002/dad2.12035. PMID: 32587882; PMCID: PMC7308793.

[120] Triantafyllou A, Ferreira JP, Kobayashi M, Micard E, Xie Y, Kearney-Schwartz A et al. Longer Duration of Hypertension and MRI Microvascular Brain Alterations Are Associated with Lower Hippocampal Volumes in Older Individuals with Hypertension. *J Alzheimers Dis*. 2020;74(1):227-235. doi: 10.3233/JAD-190842. PMID: 32039844; PMCID: PMC7175941.

[121] Naing HL, Teo SP. Impact of Hypertension on Cognitive Decline and Dementia. *Ann Geriatr Med Res*. 2020 Mar;24(1):15-19. doi: 10.4235/agmr.19.0048. Epub 2020 Mar 18. PMID: 32743317; PMCID: PMC7370774.

[122] Chau ACM, Cheung EYW, Chan KH, Chow WS, Shea YF, Chiu PKC et al. Impaired cerebral blood flow in type 2 diabetes mellitus - A comparative study with subjective cognitive decline, vascular dementia and Alzheimer's disease subjects. *Neuroimage Clin*. 2020;27:102302. doi: 10.1016/j.nicl.2020.102302. Epub 2020 May 28. PMID: 32521474; PMCID: PMC7284123.

[123] Endemann DH, Schiffrin EL. Endothelial dysfunction. *J Am Soc Nephrol*. 2004 Aug;15(8):1983-92. doi: 10.1097/01.ASN.0000132474.50966.DA. PMID: 15284284.

[124] Martinez-Quinones P, McCarthy CG, Watts SW, Klee NS, Komic A, Calmasini FB et al. Hypertension Induced Morphological and Physiological Changes in Cells of the Arterial Wall. *Am J Hypertens*. 2018 Sep 11;31(10):1067-1078. doi: 10.1093/ajh/hpy083. PMID: 29788246; PMCID: PMC6132119.

[125] Falkner B. Cardiac Output Versus Total Peripheral Resistance. *Hypertension*. 2018 Nov;72(5):1093-1094. doi: 10.1161/HYPERTENSIONAHA.118.11963. PMID: 30354830.

[126] Touyz RM, Alves-Lopes R, Rios FJ, Camargo LL, Anagnostopoulou A, Arner A et al. Vascular smooth muscle contraction in hypertension. *Cardiovasc Res*. 2018 Mar 15;114(4):529-539. doi: 10.1093/cvr/cvy023. PMID: 29394331; PMCID: PMC5852517.

[127] Urbina EM, Khoury PR, McCoy C, Daniels SR, Kimball TR, Dolan LM. Cardiac and vascular consequences of pre-hypertension in youth. *J Clin Hypertens* (Greenwich). 2011 May;13(5):332-42. doi: 10.1111/j.1751-7176.2011.00471.x. Epub 2011 Apr 21. PMID: 21545394; PMCID: PMC3092159.

[128] Tomiyama H, Ishizu T, Kohro T, Matsumoto C, Higashi Y, Takase B et al. Longitudinal association among endothelial function, arterial stiffness and subclinical organ damage in hypertension. *Int J Cardiol*. 2018 Feb 15;253:161-166. doi: 10.1016/j.ijcard.2017.11.022. Epub 2017 Nov 12. PMID: 29174285.

[129] Prencipe G, Pellegrino L, Vairo F, Tomaiuolo M, Furio OA. Dolicoarteriopatie (kinking, coiling, tortuosità) delle arterie carotidi e fattori di rischio cardiovascolare [Dolichoarteriopathy (kinking, coiling,tortuosity) of the carotid arteries and cardiovascular risk factors]. *Minerva Cardioangiol*. 1998 Jan-Feb;46(1-2):1-7. Italian. PMID: 9780615.

[130] Strecker C, Krafft AJ, Kaufhold L, Hüllebrandt M, Weber S, Ludwig U et al. Carotid geometry is an independent predictor of wall thickness - a 3D cardiovascular magnetic resonance study in patients with high cardiovascular risk. *J Cardiovasc Magn Reson*. 2020 Sep 10;22(1):67. doi: 10.1186/s12968-020-00657-5. PMID: 32912285; PMCID: PMC7488078.

[131] Yamazaki M, Uchiyama S. [Pathophysiology of carotid stenosis]. *Brain Nerve*. 2010 Dec;62(12):1269-75. Japanese. PMID: 21139179.

[132] Wang L, Zhao F, Wang D, Hu S, Liu J, Zhou Z et al. Pressure Drop in Tortuosity/Kinking of the Internal Carotid Artery: Simulation and Clinical Investigation. *Biomed Res Int*. 2016;2016:2428970. doi: 10.1155/2016/2428970. Epub 2016 Apr 18. PMID: 27195283; PMCID: PMC4852326.

[133] Shang K, Chen X, Cheng C, Luo X, Xu S, Wang W et al. Arterial Tortuosity and Its Correlation with White Matter Hyperintensities in Acute Ischemic Stroke. *Neural Plast*. 2022 Mar 24;2022:4280410. doi: 10.1155/2022/4280410. PMID: 35369646; PMCID: PMC8970938.