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REVIEW ARTICLE

Hypertension, seizures, and epilepsy: a review on pathophysiology and management

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Abstract

Background Epilepsy and hypertension are common chronic conditions, both showing high prevalence in older age groups. This review outlines current experimental and clinical evidence on both direct and indirect role of hypertension in epileptogenesis and discusses the principles of drug treatment in patients with hypertension and epilepsy.

Methods We selected English-written articles on epilepsy, hypertension, stroke, and cerebrovascular disease until December, 2018.

Results Renin-angiotensin system might play a central role in the direct interaction between hypertension and epilepsy, but other mechanisms may be contemplated. Large-artery stroke, small vessel disease and posterior reversible leukoencephalopathy syndrome are hypertension-related brain lesions able to determine epilepsy by indirect mechanisms. The role of hypertension as an independent risk factor for post-stroke epilepsy has not been demonstrated. The role of hypertension-related small vessel disease in adult-onset epilepsy has been demonstrated. Posterior reversible encephalopathy syndrome is an acute condition, often

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caused by a hypertensive crisis, associated with the occurrence of acute symptomatic seizures. Chronic antiepileptic treatment should consider the risk of drug-drug interactions with antihypertensives.

Conclusions Current evidence from preclinical and clinical studies supports the vision that hypertension may be a cause of seizures and epilepsy through direct or indirect mechanisms. In both post-stroke epilepsy and small vessel disease-associated epilepsy, chronic antiepileptic treatment is recommended. In posterior reversible encephalopathy syndrome blood pressure must be rapidly lowered and prompt antiepileptic treatment should be initiated.

Keywords Hypertension · Stroke · Posterior reversible encephalopathy syndrome · Seizures · Epilepsy

Introduction

Epilepsy and hypertension are common chronic conditions, both showing high prevalence in older age groups. Hypertension is a major risk factor for cerebrovascular diseases [1] that are the leading etiology of epilepsy in the elderly [2–4]. In this context, hypertension acts with indirect mechanisms (i.e., mediated by hypertension-related brain lesions) (Fig. 1). Epilepsy may follow a well-defined ischemic or hemorrhagic lesion (post-stroke epilepsy) (Fig. 2) or may be associated with small vessel disease (SVD) (Fig. 3). About half of unprovoked seizures (i.e., seizures not occurring during or immediately after an acute causative event) [5] may have no identifiable origin in adults [6]. Recent evidence suggests that hypertension itself can act with a direct mechanism (Fig. 1), i.e., in the absence of obviously epileptogenic brain lesions, being an independent risk factor for epilepsy [7]. Lastly, hypertension favors cerebral conditions that are frequently associated with acute symptomatic seizures, such as "posterior reversible encephalopathy syndrome" (PRES) (Fig. 4). [8]

This review delineates current experimental and clinical evidence on both direct and indirect role of hypertension in epileptogenesis and discusses the principles of drug treatment in patients with hypertension and epilepsy.

Review of the literature

Medical publications concerning seizures and epilepsy related to hypertension were reviewed. References were identified by searches of PubMed and Google Scholar until December 2018 with the terms "epileps*" or "seizur*" in various combination with "hypertension," "blood pressure," "cerebrovascular disease," "stroke," "hemorrhage," "lacunar infarction," "leukoaraiosis," "small vessel disease," "PRES," "anticonvulsants," "antihypertensive." Articles were also identified through searches of the authors' own files. Selection criteria were English language, novelty, importance, originality, quality and relevance to the scope of this review.

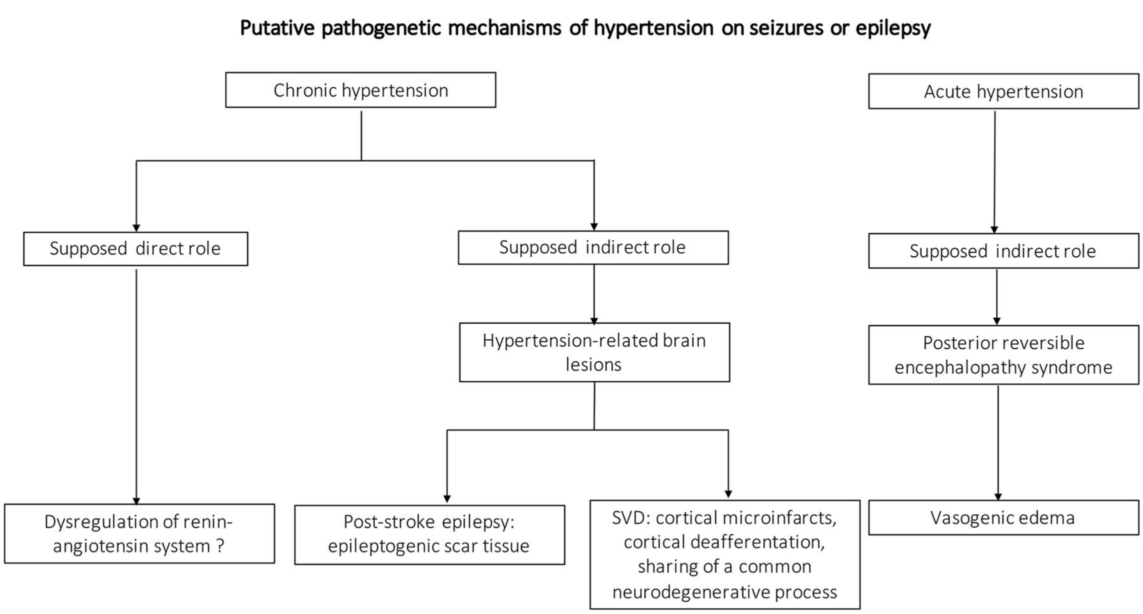

Fig. 1 Putative pathogenetic mechanisms of hypertension on seizures or epilepsy. SVD: small vessel disease

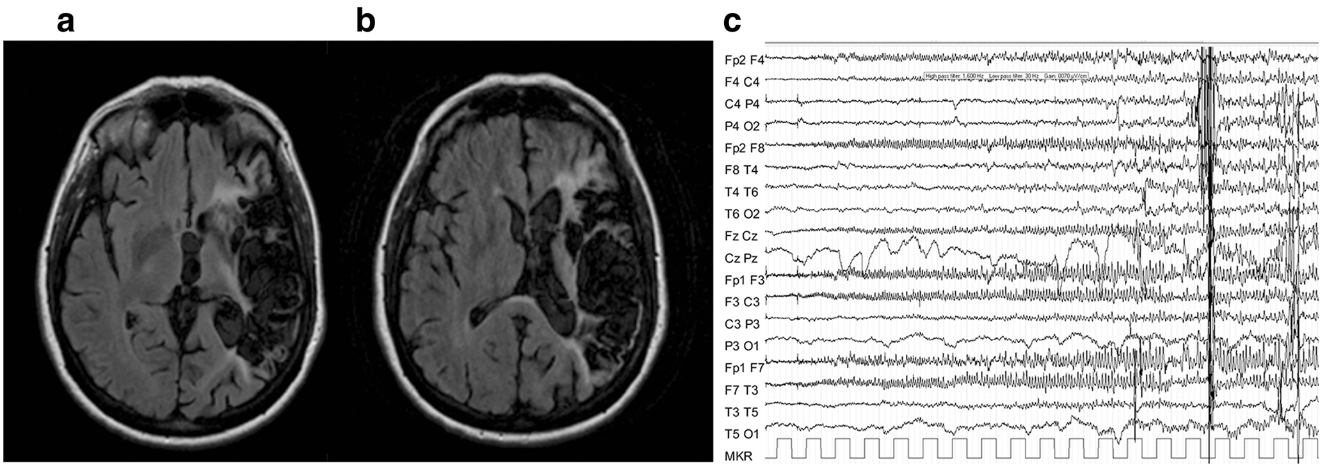

Fig. 2 Example of PSE: MRI (fluid attenuated inversion recovery: **a**, **b** showing a large stroke in the territory of left middle cerebral artery and EEG **c** showing an epileptic seizure arising from left fronto-temporal derivations

Hypertension, seizures and epilepsy: pathogenetic mechanisms

We found evidence that hypertension, either representing a chronic disorder or occurring acutely in the setting of a hypertensive crisis, may cause epileptic seizures. Chronic hypertension may directly be responsible for unprovoked seizures, and indirect mechanisms may be associated to the occurrence of acute symptomatic or unprovoked seizures. Lastly, acute hypertension may be responsible for acute symptomatic seizures through an indirect mechanism. The putative pathogenetic mechanisms of hypertension on seizures or epilepsy are summarized in Fig. 1.

Direct association

The pathophysiology of epilepsy due to hypertension has been investigated in several preclinical studies. Experimental data on different rat models of epilepsy suggest upregulation of the renin-angiotensin system (RAS), classically involved in blood pressure regulation [9]. In particular, during repetitive seizures, angiotensin II type 1 receptor and angiotensin-converting enzyme are upregulated in the hippocampus of Wistar audiogenic rats [10]. Similarly, spontaneously hypertensive rats (SHR) develop seizures with lower doses of kainic acid, compared to non-hypertensive rats [11]. In rat models of comorbid epilepsy and hypertension, treatment with anti-hypertensive drugs (namely the AT1 antagonist losartan) delayed seizures onset and reduced seizure frequency, with an effect partially independent from blood pressure modifications [10]. Reduction of seizure frequency persisted after treatment discontinuation, suggesting a role of RAS modulation in seizure prevention [12]. From a molecular point of view, losartan was able to counteract seizures-induced overexpression of AT1 receptor and to prevent seizures-related increase of hippocampal monoamine levels [11–13]. These results support the theory that angiotensin acts as a neurotransmitter or neuromodulator in specific cerebral pathways, either directly exerting its effect on specific receptors, or closely interacting with dopaminergic and GABAergic systems [9]. RAS involvement in the pathophysiologic mechanisms underlying epileptogenesis is also

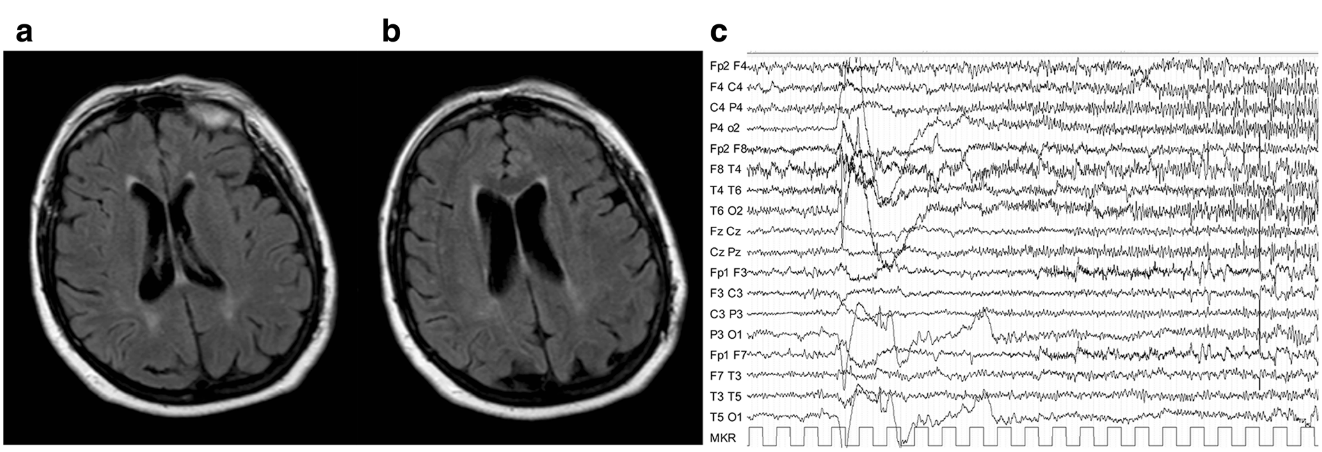

Fig. 3 Example of epilepsy associated with SVD: MRI (fluid attenuated inversion recovery: **a**, **b** showing small white matter lesions and EEG **c** showing an epileptic seizure arising from right fronto-temporal derivations

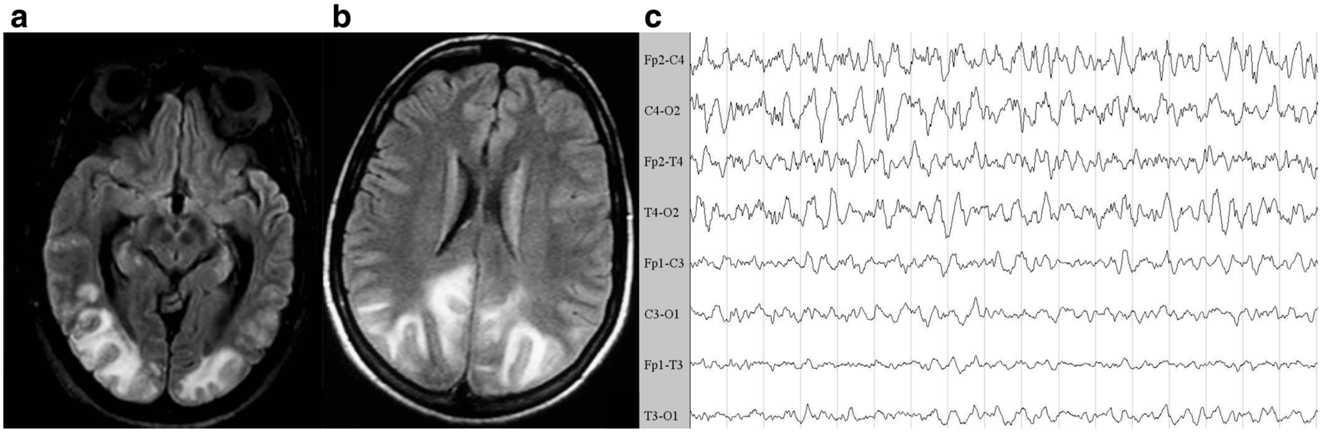

Fig. 4 Example of PRES: MRI (fluid attenuated inversion recovery: **a**, **b** showing increased white/gray matter predominantly affecting the parieto-occipital areas (right greater than left) and EEG **c** showing high-voltage delta activity over the right hemisphere

supported by a neuropathologic study showing upregulation of AT1 and AT2 receptors in the hippocampus of patients with drug-resistant temporal lobe epilepsy who underwent anteromesial temporal lobectomy [14]. The role of arterial hypertension as an independent risk factor for unprovoked seizures has been investigated in different clinical studies. A prospective cohort study evaluated midlife risk factors associated with late-onset epilepsy on 15,792 participants followed for about 20 years, finding that hypertension was associated with a hazard ratio of 1.26 (1.05–1.51, CI 95%) for late-onset epilepsy [7]. A case–control study on 227 subjects with first unprovoked seizures and 294 controls showed that a personal history of hypertension was an independent risk factor (OR = 1.57) for new-onset remote seizures, even after adjustment for cerebrovascular disease [15]. In line with these results, a cross-sectional, case-control study on 4944 subjects (65 of whom had epilepsy) highlighted the role of hypertension as an independent risk factor for epilepsy [16], since the presence of left ventricular hypertrophy (LVH) was associated with a threefold increase of the risk of epilepsy (OR = 2.9). Given the cross-sectional nature of this study, pathogenic inferences are limited. Interestingly, a population-based case-control study on 435 subjects [17] found that LVH (a consequence of severe, uncontrolled chronic hypertension) was associated with an 11-fold increased risk of unprovoked seizures of unknown etiology in comparison with controls. This risk was eliminated by diuretic treatment independently from blood pressure values.

Indirect association

Seizures associated with stroke: acute symptomatic seizures and “post-stroke epilepsy”

Hypertension is a well-known risk factor for stroke. A large multicenter case-control study [1] found that a history of hypertension was associated with an increased risk of stroke (OR 2.64, 99% CI 2.26–3.08). In the same study, population-attributable risk (i.e., the proportion of all cases which can be attributed to the specific risk factor) of hypertension for stroke was 34.6%, (99% CI 30.4–39.1). Seizures associated with stroke may occur as acute symptomatic or unprovoked seizures [4]. Acute symptomatic seizures are the result of an acute ischemic injury, leading to glutamate excitotoxicity with intracellular calcium accumulation, transmembrane depolarization and lowering of the seizure threshold [18, 19]. The pathophysiology of PSE relies on neuronal hyperexcitability and hypersynchrony, secondary to changes of membrane properties, deafferentation, selective neuronal loss, and collateral sprouting [20]. As regards parenchymal hemorrhage, products derived from blood catabolism, such as iron and hemosiderin, are epileptogenic. This was demonstrated both in animal models and in patients with ruptured vascular malformations [21, 22]. The role of cortical hyperexcitability in PSE has been studied on animal models, namely mechanical middle cerebral artery occlusion (MCAO) and photothrombosis [23–25]. Moreover, excitability of the cortical area around the vascular scar has been studied in humans by means of transcranial magnetic stimulation (TMS). In particular, a study on a cohort of subjects with stroke involving the primary motor cortex showed significant decrease of the TMS-induced silent period duration in the affected limb, when compared to the contralateral one, in 5/6 PSE-patients and in none of 76 controls without PSE [26]. In line with these results, another study revealed increased intracortical facilitation and larger amplitude of TMS-induced motor-evoked potentials in the affected hemisphere as compared to the contralateral hemisphere in 18 PSE patients but not in 18 stroke patients without epilepsy [27]. Longitudinal studies [28, 29] found that cortical involvement, hemorrhage, and acute symptomatic seizures lead to an increased risk of PSE, while age and gender do not seem to play a role. These date were confirmed in a recent meta-analysis [4]. Hypertension has been evaluated in different studies as an independent predictor of acute symptomatic post-stroke seizures [30–34] and PSE

[35–39]. In none of these studies, most of which involving both patients with ischemic and hemorrhagic stroke, hypertension was independently associated with an increased risk for PSE. Two studies on patients with intracranial hemorrhage [38, 39] led to opposite conclusions on the role of chronic hypertension in causing seizures. In particular, Ohman [38] studied prospectively the incidence and risk factors of seizures in patients who underwent surgery for aneurismal subarachnoid hemorrhage, finding that the proportion of subjects with hypertension was significantly higher among those with post-surgery seizures than among those without seizures ($p < 0.0001$). By contrast, a retrospective study on patients with intracerebral hemorrhage [39] found that pre-existing hypertension was associated with a lower risk of developing PSE. In conclusion, these data indicate that hypertension may indirectly lead to epilepsy as it represents a major risk factor for stroke. However, evidence on the role of chronic hypertension as an independent risk factor for PSE is lacking.

Seizures associated with small vessel disease

SVD is a condition affecting the smallest cerebral blood vessels, such as the perforating arterioles, capillaries, and venules. Although its pathogenesis is still incompletely understood, literature highlights that the degeneration of intraparenchymal and leptomeningeal blood vessels wall ("segmental arteriolar disorganization," "lipohyalinosis," "fibrinoid necrosis," etc) and consequent perivascular edema is crucial [40–42]. The term "leukoaraiosis" indicates round-shaped, isolated or confluent lesions, which are visible as hypodensities at CT scan and as hyperintense areas in T2 and FLAIR sequences and iso−/hypo-intense on T1 sequences at MRI. They are not cavitated and are localized in periventricular areas or deep white matter [42]. Leukoaraiosis originates from SVD causing small deep infarcts, and it is a common finding among subjects with vascular risk factors including hypertension [42–45]. Of note, the effects of small vessel lesions can be observed not only in the surrounding of the lesion, but also in remote brain areas, including connected cortical regions [43]. Moreover, SVD can cause cortical microinfarcts that are visible with advanced neuroimaging techniques [43, 46]. The role of hypertension in SVD, as well as the association between hypertension-related SVD and seizures, has been assessed in preclinical studies. A study on SHR (representing animal models of hypertension-related SVD) comprised two models of focal, temporal lobe (by amygdala kindling) and generalized (by pentylenetetrazole-induced kindling) seizures [47]. This study has shown that SVD predisposes to temporal lobe epilepsy but not to generalized seizures, and that this susceptibility can be avoided by pre-treatment with enalapril [47]. Similarly, another study [11] showed greater susceptibility to kainate-induced status epilepticus for SHR compared to control rats, and delayed seizures onset in SHR after administration of losartan. The association between hypertension, SVD and seizures has been assessed also in clinical studies. Seizures and epilepsy associated with SVD have been considered uncommon by some authors [48, 49], but these findings derived from studies with methodological limits (i.e., small sample size in [48]; absence of MRI investigation in [49]). In a retrospective study on 223 consecutive subjects with SVD [50], hypertension was positively associated with cerebral lesion load ($p < 0.001$), and seizures manifested in 24% of patients, especially those with frontal or parieto-occipital lesions. The authors hypothesize that subcortical white matter lesions may involve U-fibers, increasing the propensity for seizures. Similarly, another retrospective work [51] found higher prevalence and more severe SVD in a group of 105 patients with late-onset (i.e., after 60 years old) epilepsy, compared to a group of 105 controls. This finding was independent from pre-existing clinical strokes, suggesting a possible epileptogenic role for SVD. However, about half of the patients included in the study did not undergo brain MRI, thus limiting the generalizability of results. Two retrospective studies with overlapping population [52, 53] examined the incidence and predictors of seizures and epilepsy in patients with lacunar stroke. The first study [52] found that neither the presence of vascular risk factors including hypertension, nor the degree of white matter changes were associated with the development of epilepsy. The second study [53] on 292 subjects with lacunar strokes found that 44 patients with seizures had a lower main National Institute of Health Stroke Scale score ($p = 0.00133$) and a lower Mini Mental State Examination score ($p < 0.001$) as compared to 248 patients without seizures. These authors conclude that the seizures were more linked to the cognitive status than to SVD, postulating that an underlying neurodegenerative process may be responsible for seizures and cognitive impairment. However, many patients did not undertake brain MRI, limiting the generalizability of results. Moreover, cognitive status was assessed after the onset of epilepsy, in patients with ongoing AED treatment, thus it was impossible to establish whether the cognitive decline was pre-existing to seizures or to stroke, or was influenced by treatment. Another retrospective study [54] found significant differences in electroclinical semiology between PSE and epilepsy associated with SVD. In particular, temporal lobe epilepsy was more frequent in patients with epilepsy associated with SVD, even though white matter lesions were evenly distributed. The authors hypothesized a specific susceptibility of temporal structures to the development of seizures in the context of SVD, thus suggesting the existence of different pathogenetic mechanisms between PSE and epilepsy associated with SVD. Of note, three patients with hypertensive encephalopathy followed by temporal lobe epilepsy due to hippocampal sclerosis were described [55]. A susceptibility of temporal lobe structures to hypertension-induced damage might be hypothesized.

In conclusion, both preclinical and clinical data suggest that hypertension-related SVD might play a pathogenic role in otherwise unexplained adult-onset epilepsy. Possible pathogenic mechanisms may include the presence of cortical microinfarcts as well as the effects of cortical deafferentation due to white matter lesions on surrounding or remote areas. Alternatively, both SVD and epilepsy may share a common neurodegenerative process that remains to be elucidated.

Seizures associated with PRES

PRES is a potentially reversible clinical condition deriving from blood–brain barrier dysfunction, vascular leakage and, then, vasogenic edema [56–58]. Although cerebrovascular autoregulation is able to maintain a constant cerebral blood flow independently from systemic blood pressure fluctuations, a sudden increase of blood pressure above the upper autoregulatory limit may lead to cerebral hyperperfusion [57, 58]. In experimental studies, a systemic inflammatory response mediated by cytokine release has been demonstrated in PRES [59]. Among cytokines, the proinflammatory TNF-α, IL-1, IL-6, and INF-γ result in T cell activation and increased leukocyte adhesion and activation, contributing to vasogenic edema [59]. Focal or focal-to-bilateral seizures occur in about two thirds of subjects as a result of vasogenic edema [60, 61]. PRES is very frequent in patients with eclampsia, presenting during pregnancy or post-partum with hypertension, proteinuria, peripheral edema, and epileptic seizures. In different retrospective studies [62, 63], clinical and radiological features of PRES were present in 50–98% of women with eclampsia who underwent MRI. This high incidence probably reflects a selection bias, since the decision to perform neuroimaging was based on the physician's judgment, probably in the presence of focal neurological signs. In 3–13% of cases, seizures may result in status epilepticus, which is one of the most severe complications of PRES [61, 64]. Although PRES causes acute symptomatic seizures, a minority of subjects (2–4%) may experience long-term recurrence [65–67], thus configuring PRES-related epilepsy.

Hypertension, seizures, and epilepsy: treatment strategies

Antiepileptic treatment in patients with chronic hypertension and seizures

The coexistence of chronic hypertension and epilepsy exposes patients to multiple drug treatments. This implies careful management, especially in the elderly population [68, 69], as the probability of drug-drug interactions, both pharmacokinetic and pharmacodynamic, rise with the number of introduced drugs. Enzyme-inducing AEDs, namely carbamazepine, phenobarbital, and phenytoin may increase liver metabolism and consequently reduce serum levels of other drugs, including antihypertensives [70]. Beta-blockers (propranolol, timolol), calcium antagonists (verapamil, amlodipine, felodipine, nifedipine), and sartans (losartan, irbesartan) are the drugs most frequently involved in pharmacokinetic interactions, often resulting in reduced levels of antihypertensives [70]. In some cases, the use of calcium antagonists may increase plasmatic levels of carbamazepine or phenytoin, inducing toxicity [71]. In conclusion, interactions between AEDs and antihypertensives might be clinically relevant and should be considered in cases of toxicity or difficult-to-treat hypertension. Newer, non-enzyme inducing AEDs might be preferred in patients with hypertension [70].

Antiepileptic treatment in patients with acute hypertension and acute symptomatic seizures

PRES and eclampsia are characterized by acute hypertension. In these conditions, rapid blood pressure lowering and seizure control must be sought at the same time. The most used antihypertensive drugs include easily titratable agents administered intravenously, like calcium antagonists (clevidipine, nicardipine), beta-blockers (labetalol), and nitrates (nitroprusside) [8]. All are safe and effective in reducing blood pressure. AED treatment should also be promptly initiated, taking into account renal function and comorbidities [8]. Treatment discontinuation should follow clinical and neuroimaging normalization. Eclampsia deserves a specific treatment. In this condition, magnesium sulfate is the drug of choice, since randomized controlled trials have shown its efficacy and safety in preventing seizure recurrence during eclampsia [72]. The mechanism of action of magnesium sulfate is not fully understood, but evidence from animal models [73] indicate that, in pregnant mice with ischemic placenta and endothelial dysfunction, magnesium sulfate increased epileptic threshold, measured by susceptibility to pentylenetetrazole-induced seizures. In mice treated with magnesium sulfate, brain blood barrier permeability and microglial activation were reduced as compared to control animals [73]. Thus, magnesium sulfate may represent an etiological treatment for seizures in the context of eclampsia. In a case series, PRES has been associated with hypomagnesemia [74], and the use of magnesium sulfate for PRES treatment has been reported [75] with encouraging results. Further studies are needed to elucidate the efficacy of this treatment.

Conclusions

Both epilepsy and hypertension are frequent, chronic diseases that can coexist in the same individual. The pathogenic role of hypertension in determining seizures and epilepsy may be direct or indirect. Renin-angiotensin system might play a central role in the direct interaction between hypertension and epilepsy: this is supported by the observation that drugs able to block RAS prevent seizures in animal models. Moreover, hypertension is a predictor of late-onset epilepsy independently from vascular damage. Hypertension may also act indirectly by promoting cerebrovascular diseases, such as stroke or PRES, that predispose to acute symptomatic seizures or chronic epilepsy. Data from literature indicate that hypertension is not an independent risk factor for PSE. SVD is most often related to chronic hypertension, and both experimental and clinical data support a role of SVD in the development of otherwise unexplained adult-onset epilepsy. Pharmacological treatment in patients with hypertension and seizures should take into account drug-drug interactions and mechanisms of action. During PRES, blood pressure must be rapidly lowered and AED treatment should be promptly initiated. Magnesium sulfate is largely used as anticonvulsant during eclampsia and its use in PRES needs to be explored.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Dans AL, Yusoff K, Truelsen T, Diener HC, Sacco RL, Ryglewicz D, Czlonkowska A, Weimar C, Wang X, Yusuf S (2010) Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the interstroke study): a case-control study. Lancet 376:112–123
2. Paradowski B, Zagrajek MM (2005) Epilepsy in middle-aged and elderly people: a three-year observation. Epileptic Disord 7(2):91–95
3. Cloyd J, Hauser W, Towne A et al (2006) Epidemiological and medical aspects of epilepsy in the elderly. Epilepsy Res 68(Suppl 1):S39–S48
4. Ferlazzo E, Gasparini S, Beghi E, Epilepsy Study Group of the Italian Neurological Society et al (2016) Epilepsy in cerebrovascular diseases: review of experimental and clinical data with meta-analysis of risk factors. Epilepsia 57(8):1205–1214
5. Beghi E, D'Alessandro R, Beretta et al. (2011) Incidence and predictors of acute symptomatic seizuresafter stroke. Neurology 77: 1785—1793
6. Hauser WA, Annegers JF, Kurland LT (1993) Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia 34:453–468
7. Johnson EL, Krauss GL, Lee AK et al (2018) Association between midlife risk factors and late-onset epilepsy: results from the atherosclerosis risk in communities study. JAMA Neurol 1;75(11):1375–1382
8. Neill TA. Posterior reversible encephalopathy syndrome. UpToDate inc, Wolters Kluver eds. https://www.uptodate.com/contents/reversible-posterior-leukoencephalopathy-syndrome?search=pres&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H1336824701. Updated Nov 19, 2018, accessed on Jan 24, 2019
9. Tchekalarova J, Georgiev V (2005) Angiotensin peptides modulatory system: how is it implicated in the control of seizure susceptibility? Life Sci 14;76(9):955–970
10. Pereira MG, Becari C, Oliveira JA et al (2010) Inhibition of the renin-angiotensin system prevents seizures in a rat model of epilepsy. Clin Sci (Lond) 17;119(11):477–482
11. Tchekalarova J, Loyens E, Smolders I (2015) Effects of AT1 receptor antagonism on kainate-induced seizures and concomitant changes in hippocampal extracellular noradrenaline, serotonin, and dopamine levels in Wistar-Kyoto and spontaneously hypertensive rats. Epilepsy Behav 46:66–71
12. Tchekalarova JD, Ivanova N, Atanasova D, Pechlivanova DM, Lazarov N, Kortenska L, Mitreva R, Lozanov V, Stoynev A (2016) Long-term treatment with losartan attenuates seizure activity and neuronal damage without affecting behavioral changes in a model of co-morbid hypertension and epilepsy. Cell Mol Neurobiol 36(6):927–941
13. Atanasova D, Tchekalarova J, Ivanova N et al (2018) Losartan suppresses the kainate-induced changes of angiotensin AT1 receptor expression in a model of comorbid hypertension and epilepsy. Life Sci 15(193):40–46
14. Arganaraz GA, Konno AC, Perosa SR et al (2008) The renin-angiotensin system is upregulated in the cortex and hippocampus of patients with temporal lobe epilepsy related to mesial temporal sclerosis. Epilepsia 49:1348–1357
15. Ng SK, Hauser WA, Brust JC et al (1993) Hypertension and the risk of new-onset unprovoked seizures. Neurology 43:425–428
16. Li X, Breteler MM, deBruyne MC et al (1997) Vascular determinants of epilepsy: the Rotterdam Study. Epilepsia 38:1216–1220
17. Hesdorffer TCC, Hauser WA, Annegers JF et al (1996) Severe, uncontrolled hypertension and adult-onset seizures: a case-control study in Rochester, Minnesota. Epilepsia 37(8):736–741
18. Lambrakis CC, Lancman ME (1998) The phenomenology of seizures and epilepsy after stroke. J Epilepsy 11:233–240
19. Silverman IE, Restrepo L, Mathews GC (2002) Poststroke Seizures. Arch Neurol 59(2):195–201
20. Menon B, Shorvon SD (2009) Ischaemic stroke in adults and epilepsy. Epilepsy Res 87:1–11
21. Rosen AD, Frumin NV (1979) Focal epileptogenesis after intracortical hemoglobin injection. Exp Neurol 66:277–284
22. Moran NF, Fish DR, Kitchen N, Shorvon S, Kendall BE, Stevens JM (1999) Supratentorial cavernous haemangiomas and epilepsy: a review of the literature and case series. J Neurol Neurosurg Psychiatry 66:561–568
23. Watson BD, Dietrich WD, Busto R, Wachtel MS, Ginsberg MD (1985) Induction of reproducible brain infarction by photochemically initiated thrombosis. Ann Neurol 17:497–504
24. Karhunen H, Bezvenyuk Z, Nissinen J et al (2007) Epileptogenesis after cortical photothrombotic brain lesion in rats. Neuroscience 48: 314–324

25. Cuomo O, Rispoli V, Leo A, Politi GB, Vinciguerra A, di Renzo G, Cataldi M (2013) The antiepileptic drug levetiracetam suppresses non-convulsive seizure activity and reduces ischemic brain damage in rats subjected to permanent middle cerebral artery occlusion. PLoS One 8:e80852
26. Kessler KR, Schnitzler A, Classen J, Benecke R (2002) Reduced inhibition within primary motor cortex in patients with poststroke focal motor seizures. Neurology 59:1028–1033
27. Kim JH, Lee HW, Cohen LG, Park KD, Choi KG (2008) Motor cortical excitability in patients with poststroke epilepsy. Epilepsia 49:117–124
28. Serafini A, Gigli GL, Gregoraci G, Janes F, Cancelli I, Novello S, Valente M (2015) Are early seizures predictive of epilepsy after a stroke? Results of a population-based study. Neuroepidemiology 45:50–58
29. Galovic M, Döhler N, Erdélyi-Canavese B, Felbecker A, Siebel P, Conrad J, Evers S, Winklehner M, von Oertzen TJ, Haring HP, Serafini A, Gregoraci G, Valente M, Janes F, Gigli GL, Keezer MR, Duncan JS, Sander JW, Koepp MJ, Tettenborn B (2018) Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study. The Lancet Neurology 17:143–152
30. Labovitz DL, Hauser WA, Sacco RL (2001) Prevalence and predictors of early seizure and status epilepticus after first stroke. Neurology 57:200–206
31. Alberti A, Paciaroni M, Caso V et al (2008) Early seizures in patients with acute stroke: frequency, predictive factors, and effect on clinical outcome. Vasc Health Risk Manag 4:715–720
32. De Herdt V, Dumont F, Henon H et al (2011) Early seizures in intracerebral hemorrhage: incidence, associated factors, and outcome. Neurology 77:1794–1800
33. Procaccianti G, Zaniboni A, Rondelli F, Crisci M, Sacquegna T (2012) Seizures in acute stroke: incidence, risk factors and prognosis. Neuroepidemiology 39:45–50
34. Goswami RP, Karmakar PS, Ghosh A (2012) Early seizures in first-ever acute stroke patients in India: incidence, predictive factors and impact on early outcome. Eur J Neurol 19:1361–1366
35. Awada A, Omojola MF, Obeid T (1999) Late epileptic seizures after cerebral infarction. Acta Neurol Scand 99:265–268
36. Lossius MI, Rønning OM, Mowinckel P, Gjerstad L (2002) Incidence and predictors for post-stroke epilepsy. A prospective controlled trial. The Akershus stroke study. Eur J Neurol 9:365–368
37. Jungehulsing GJ, Heuschmann PU, Holtkamp M, Schwab S, Kolominsky-Rabas PL (2013) Incidence and predictors of post-stroke epilepsy. Acta Neurol Scand 127:427–430
38. Ohman J (1990) Hypertension as a risk factor for epilepsy after aneurysmal subarachnoid hemorrhage and surgery. Neurosurgery 27(4):578–581
39. Lahti AM, Saloheimo P, Huhtakangas J, Salminen H, Juvela S, Bode MK, Hillbom M, Tetri S (2017) Poststroke epilepsy in long-term survivors of primary intracerebral hemorrhage. Neurology 88: 2169–2175
40. Lammie GA, Brannan F, Wardlaw JM (1998) Incomplete lacunar infarction (type 1b lacunes). Acta Neuropathol 96:163–171
41. Muñoz Maniega S, Chappell FM, Valdés Hernández MC, Armitage PA, Makin SD, Heye AK, Thrippleton MJ, Sakka E, Shuler K, Dennis MS, Wardlaw JM (2017) Integrity of normal-appearing white matter: influence of age, visible lesion burden and hypertension in patients with small-vessel disease. J Cereb Blood Flow Metab 37(2):644–656
42. Regenhardt RW, Das AS, Lo EH et al (2018) Advances in understanding the pathophysiology of lacunar stroke: a review. JAMA Neurol 1;75(10):1273–1281
43. Ter Telgte A, van Leijsen EMC, Wiegertjes K et al (2018) Cerebral small vessel disease: from a focal to a global perspective. Nat Rev Neurol 14(7):387–398
44. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, DeCarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge R, Pantoni L, Speck O, Stephan BCM, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB, Dichgans M (2013) Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 12:822–838
45. Pantoni L, Garcia JH (1995) The significance of cerebral white matter abnormalities 100 years after Binswanger's report: a review. Stroke 26:1293–1301
46. Smith EE, Schneider JA, Wardlaw JM, Greenberg SM (2012) Cerebral microinfarcts: the invisible lesions. Lancet Neurol 11: 272–282
47. Russo E, Leo A, Scicchitano F, Donato A, Ferlazzo E, Gasparini S, Cianci V, Mignogna C, Donato G, Citraro R, Aguglia U, de Sarro G (2017) Cerebral small vessel disease predisposes to temporal lobe epilepsy in spontaneously hypertensive rats. Brain Res Bull 130: 245–250
48. Schreiner A, Pohlmann-Eden B, Schwartz A, Hennerici M (1995) Epileptic seizures in subcortical vascular encephalopathy. J Neurol Sci 130:171–177
49. Bentes C, Pimentel J, Ferro JM (2001) Epileptic seizures following subcortical infarcts. Cerebrovasc Dis 12:331–334
50. Okroglic S, Widmann CN, Urbach H, Scheltens P, Heneka MT (2013) Clinical symptoms and risk factors in cerebral microangiopathy patients. PLoS One 8(2):e53455
51. Maxwell H, Hanby M, Parkes LM, Gibson LM, Coutinho C, Emsley HCA (2013) Prevalence and subtypes of radiological cerebrovascular disease in late-onset isolated seizures and epilepsy. Clin Neurol Neurosurg 115:591–596
52. De Reuck J, Nagy E, Van Maele G (2007) Seizures and epilepsy in patients with lacunar strokes. J Neurol Sci 15;263(1–2):75–78
53. De Reuck J, Van Maele G (2009) Cognitive impairment and seizures in patients with lacunar strokes. Eur Neurol 61(3):159–163
54. Gasparini S, Ferlazzo E, Beghi E, Sofia V, Mumoli L, Labate A, Cianci V, Fatuzzo D, Bellavia MA, Arcudi L, Russo E, de Sarro G, Gambardella A, Aguglia U (2015) Epilepsy associated with Leukoaraiosis mainly affects temporal lobe: a casual or causal relationship? Epilepsy Res 109:1–8
55. Solinas C, Briellmann RS, Harvey ASETAL (2003) Hypertensive encephalopathy antecedent to hippocampal sclerosis and temporal lobe epilepsy? Neurology 60:1534–1536
56. Lassen NA (1971) Regulation of cerebral circulation. Acta Anaesthesiol Scand Suppl 45:78–80
57. Strandgaard S, Olesen J, Skinhoj E, Lassen NA (1973) Autoregulation of brain circulation in severe arterial hypertension. Br Med J 1(5852):507–510
58. Narbone MC, Musolino R, Granata F, Mazzù I, Abbate M, Ferlazzo E (2006) PRES: posterior or potentially reversible encephalopathy syndrome? Neurol Sci 27:187–189
59. Chen Z, Shen GQ, Lerner A, Gao B (2017) Immune system activation in the pathogenesis of posterior reversible encephalopathy syndrome. Brain Res Bull 131:93–99
60. Lee VH, Wijdicks EF, Manno EM et al (2008) Clinical spectrum of reversible posterior leukoencephalopathy syndrome. Arch Neurol 65(2):205–210
61. Kastrup O, Gerwig M, Frings M, Diener HC (2012) Posterior reversible encephalopathy syndrome (PRES): electroencephalographic findings and seizure patterns. J Neurol 259(7):1383–1389
62. Brewer J, Owens MY, Wallace K, Reeves AA, Morris R, Khan M, LaMarca B, Martin JN Jr (2013) Posterior reversible encephalopathy syndrome in 46 of 47 patients with eclampsia. Am J Obstet Gynecol 208:468.e1–468.e6

63. Camara-Lemarroy CR, Escobedo-Zuniga N, Villareal-Garza E et al (2017) Posterior reversible leukoencephalopathy syndrome (PRES) associated with severe eclampsia: clinical and biochemical features. Pregnancy Hypertension 7:44–49
64. Kozak OS, Wijdicks EF, Manno EM et al (2007) Status epilepticus as initial manifestation of posterior reversible encephalopathy syndrome. Neurology 69:894–897
65. Sha Z, Moran BP, McKinney AM et al (2015) Seizure outcomes of posterior reversible encephalopathy syndrome and correlations with electroencephalographic changes. Epilepsy Behav 48:70–74
66. Datar S, Singh T, Rabinstein AA, Fugate JE, Hocker S (2015) Long-term risk of seizures and epilepsy in patients with posterior reversible encephalopathy syndrome. Epilepsia 56:564–568
67. Heo K, Cho KH, Lee MK, Chung SJ, Cho YJ, Lee BI (2016) Development of epilepsy after posterior reversible encephalopathy syndrome. Seizure 34:90–94
68. Ferlazzo E, Sueri C, Gasparini S, Aguglia U (2016) Challenges in the pharmacological management of epilepsy and its causes in the elderly. Pharmacol Res 106:21–26
69. Leporini C, De Sarro G, Russo E (2014) Adherence to therapy and adverse drug reactions: is there a link? Exp Opin Drug Safety 13(Suppl 1):S41–S55
70. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D (2013) Enzyme induction with antiepileptic drugs: cause for concern? Epilepsia 54:11–27
71. Bahls FH, Ozuna J, Ritchie DE (1991) Interactions between calcium channel blockers and the anticonvulsants carbamazepine and phenytoin. Neurology 41:740–742
72. Sibai BM (2004) Magnesium sulfate prophylaxis in preeclampsia: lessons learned from recent trials. Am J Obstet Gynecol 190:1520–1526
73. Johnson AC, Tremble SM, Chan SL, Moseley J, LaMarca B, Nagle KJ, Cipolla MJ (2014) Magnesium sulfate treatment reverses seizure susceptibility and decreases neuroinflammation in a rat model of severe preeclampsia. PLoS One 9:e113670
74. Chardain A, Mesnage V, Alamowitch S, Bourdain F, Crozier S, Lenglet T, Psimaras D, Demeret S, Graveleau P, Hoang-Xuan K, Levy R (2016) Posterior reversible encephalopathy syndrome (PRES) and hypomagnesemia: a frequent association? Rev Neurol 172(6–7):384–388
75. Pandita A, Lehmann DF (2018) Magnesium sulfate treatment correlates with improved neurological function in posterior reversible encephalopathy syndrome (PRES). Neurologist 23(2):65–66