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REVIEW

Post-epilepsy stroke: A review

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ABSTRACT

Stroke and epilepsy are two of the most common neurological disorders and share a complicated relationship. It is well established that stroke is one of the most important causes of epilepsy, particularly new-onset epilepsy among the elderly. However, post-epilepsy stroke has been overlooked. In recent years, it has been demonstrated that epilepsy patients have increased risk and mortality from stroke when compared with the general population. Additionally, it was proposed that post-epilepsy stroke might be associated with antiepileptic drugs (AEDs), epileptic seizures and the lifestyle of epileptic patients. Here, we comprehensively review the epidemiology, causes and interventions for post-epilepsy stroke.

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Introduction

Stroke and epilepsy are two of the most common, disabling neurological disorders in the world [1], and the relationship between them is complicated. Early in 1864, epilepsy after stroke was first described by Hughlings Jackson [2]. Today, cerebral stroke is viewed as one of the most important causative factors for new-onset epilepsy, particularly among the elderly [3]. Poststroke epilepsy has been comprehensively studied. In contrast, stroke after epilepsy, or postepilepsy stroke, is not well understood.

A large number of epidemiological studies have suggested that epilepsy patients face a much higher risk of stroke (both ischemic and hemorrhagic stroke) than does the general population [4–7]. Additional studies have further demonstrated that epilepsy patients show increased mortality from stroke [8–10], and stroke has been suggested to be one of the most common causes of death in epilepsy patients [8,10–12]. Thus far, several possible reasons for postepilepsy stroke have been proposed. Antiepileptic drugs (AEDs) exposure, epileptic seizures, and the lifestyles of epilepsy patients may contribute to the development of stroke. This review summarizes the epidemiology of and possible reasons for postepilepsy stroke and discusses interventions for it.

Materials and methods

We performed a review of the recent literature on the epidemiology and possible reasons for postepilepsy stroke, and the interventions for postepilepsy stroke. A PubMed and Medline literature search was performed for relevant articles published prior to 2016 using the following search terms: epilepsy plus stroke, seizure plus stroke, stroke plus antiepileptic drugs. Clinical trials, animal experiments, review articles, and practice guidelines were all included.

Epidemiology of postepilepsy stroke

Increased risk of stroke in epilepsy patients

In early 1982, a study described epilepsy preceding stroke for the first time [13]. Since that investigation, several epidemiological studies have demonstrated an increased risk of stroke in epilepsy patients.

Several cohort studies have indicated that the risk of stroke is elevated in epilepsy patients. In 2004, a study by Cleary et al. showed that the relative hazard of stroke in epilepsy patients was 2.89 (95% confidence interval [CI] 2.45–3.41) [5]. In another study, Selassie et al. found that epilepsy patients had a higher risk of stroke (odds ratio [OR] = 4.20; 95% CI 4.06–4.34) compared with a control group [14]. Recently, Chang et al. conducted a population-based study by using the Taiwan National Health Insurance claims data and determined that epilepsy patients had a threefold higher risk of stroke than did a control group [4].

A similar conclusion has been reached in several cross-sectional studies. In 2004, Gaitatzis et al. found that epilepsy patients had an increased risk of stroke (OR = 6.96; 95% CI 6.38–7.60) [15]. In 2005, Tellez-Zenteno et al. concluded that epilepsy patients had a 2–5 times higher risk of stroke, with higher ORs of 3.9 (95% CI 2.7–5.3) based on the Community Health Survey and 4.7 (95% CI 3.4–6.2) based on the National Population Health Survey [6]. In 2006, another study found that epilepsy patients were 5.84 (95% CI 2.89–11.79) times more likely to suffer a stroke than the control group [16].

Case–control studies have also yielded similar results [17,18].

Increased risk of death from stroke in epilepsy patients

According to the literature from prospective to retrospective studies, mortality was higher in epileptic patients with stroke as compared to general population with stroke.

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Prospective studies have demonstrated elevated mortality from stroke in epilepsy patients. In 1994, Cockerell et al. found that stroke was one of the most common causes of death in epilepsy patients, with a standard mortality ratio (SMR) of 3.7 (95% CI 2.4–5.4) [8] (SMR here is the ratio of epileptic patients with stroke and general population died of stroke). Three years later, Nilsson similarly found an SMR of 5.3 (95% CI 4.9–5.8) for epileptic patients with stroke as compared to general population with stroke [10]. In 2006, a prospective cohort study in rural China showed that 31% of deaths in epilepsy patients were due to ischemic stroke or hemorrhagic stroke, with an age-adjusted proportional mortality rate of 30% and an SMR of 7.0 (95% CI 6.5–7.6) compared to general population with stroke [9].

In 2006, a retrospective comparative cohort study reported that the cause-specific SMRs were 1.63 (95% CI 0.82–2.89, $p = 0.10$) in newly diagnosed patients and 2.94 (95% CI 2.08–4.02, $p < 0.0001$) in chronic epilepsy patients [12].

Age and postepilepsy stroke

Numerous evidences showed that, although the stroke risk increased with age, when compared with control in the same age ranges, the younger patients tended to face higher risks of stroke.

In a case–control study performed in early 1987, Shinton et al. found that 8 of 230 patients under 70 years of age suffered postepilepsy stroke. Among these eight patients, four experienced seizures before the age of 40, two between the ages of 40 and 60, and two after the age of 60 [17]. Moreover, a retrospective cohort study reported that, compared with comparison cohorts, the highest stroke risk (HR = 8.88; 95% CI 5.71–13.82) was observed in the 20- to 39-year-old patient group. The risk of stroke was 4.89-fold (95% CI 3.83–6.26) greater in patients from 40- to 59 years old and 2.32-fold (95% CI 1.99–2.71) greater in patients above 60 years in Taiwan population [4]. Gaitatzis et al. also found that the OR of stroke was higher in younger adult patients (age 16–64 years; OR = 14.19; 95% CI 12.04–16.73) than in older patients (age >64 years; OR = 5.46; 95% CI 4.91–6.07) [15].

In 2015, a population-based retrospective cohort study showed that 48% patients having stroke subsequent to adult onset epilepsy were 35–59 years old. This result was consistent with previous findings [19].

Gender and postepilepsy stroke

A link between gender and postepilepsy stroke has been observed. A retrospective cohort study found a greater risk of stroke in male patients (HR = 1.20; 95% CI 1.01–1.51) [20]. In another retrospective cohort study in Taiwan population, Chang et al. also found that the risk of stroke was higher in male patients (adjusted hazard ratio [aHR] = 3.32; 95% CI 2.85–3.87) than in female patients (aHR = 2.35; 95% CI 1.91–2.89) [4].

Types of stroke in epilepsy patients

Thus far, most of the available data have shown that the risk of ischemic stroke is slightly higher than that of hemorrhagic stroke.

In early 1987, a case–control study showed that among eight postepilepsy stroke patients five had suffered a cerebral infarction, one had suffered a hemorrhagic stroke, one had suffered a subarachnoid hemorrhage, and one had had an unclassified stroke [17]. In 2004, a cross-sectional study found increased ORs of 10.62 for hemorrhagic strokes (95% CI 6.52–17.32), 7.49 for 'occlusive' strokes (95% CI 5.69–9.86) and 4.94 for transient ischemic attacks (95% CI 4.44–5.50) [15]. However, in a retrospective cohort study in Taiwan population, Chang et al. found that the HRs for ischemic stroke and hemorrhagic stroke were 2.85 (95% CI 2.49–3.26) and 3.30 (95% CI 2.46–4.43), respectively [4].

In one case report, multiple cerebral microbleeds were found in two patients with status epilepticus [21].

Possible causes of postepilepsy stroke

The causes of postepilepsy stroke remain unclear. It has been proposed that AEDs, epileptic seizures themselves, or the lifestyles of epilepsy patients may contribute to the development of postepilepsy stroke.

Side effects of AEDs

Because epilepsy is a chronic medical condition, most epilepsy cases require long-term therapy with AEDs [22], and refractory epilepsy patients usually require lifelong AEDs treatment [23]. On the other hand, it has been shown that the risk of stroke is elevated in patients receiving AEDs in comparison with the general population [20,24]. Moreover, the risk of stroke is higher in patients receiving AEDs than in those not receiving AEDs [24]. Furthermore, the extent to which the risk of stroke is increased varies with the AEDs that are prescribed. Thus, AEDs treatment is associated with the development of postepilepsy stroke.

In 2011, a nationwide cohort study revealed that the risk of stroke was increased in patients treated with AEDs compared with patients who were not (all p-values<0.0001) [24]. The extent of this effect varies with the AEDs prescribed. Olesen et al. and Hsieh et al. found that patients receiving carbamazepine (CBZ), oxcarbazepine (OXC), valproic acid (VPA), phenytoin (PHT), phenobarbital (PB), clonazepam, and clobazam exhibited an increased risk of stroke [20,24]. An increased risk of stroke was not observed in patients receiving lamotrigine (LTG) [24]. However, a relationship between VPA exposure and the risk of ischemic stroke was not observed in a recent case–control study [25]. Currently, minimal data are available on the effects of new-generation AEDs, except LTG and OXC, on the risk of stroke.

The use of OXC, PB, clonazepam, and clobazam has been shown to increase the risk of stroke in comparison with CBZ, while the use of LTG results in a decreased risk [20]. The effects of PHT and VPA on the risk of stroke are uncertain [20,24].

The extent to which the risk of stroke is increased may be related to AEDs doses. Chang et al. found that in Taiwan population the lowest dose of AEDs increased the risk of stroke 1.30-fold (HR = 1.30; 95% CI 1.03–1.64), whereas the highest dose of AED increased the risk of stroke 5.84-fold (HR = 5.84; 95% CI 5.02–6.80) [4]. Another study also showed

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that the relationship between the risk of stroke and PHT is dose dependent [20].Besides it is further found that the aHRs of combination of AEDs (CBZ with PHT or VPA) increased the risk of stroke (HR = 2.13, 95% CI 1.41–3.20, and HR = 1.54; 95% CI 0.84–2.83, respectively) compared to CBZ [20].

Additionally, the extent to which the risk of stroke is increased may be associated with the duration of AEDs exposure. Hsieh et al. found a greater risk of stroke in patients with longer durations of PHT exposure [20]. Similarly, Chang et al. described an increased overall risk of stroke (both ischemic and hemorrhagic stroke; $p < 0.0001$) as AED exposure increased in Taiwan population [4].

A variety of metabolic side effects that contribute to the propensity to develop a stroke have been reported among patients being treated with AEDs [26]. Lipid abnormalities, weight gain, obesity, insulin resistance (IR), hyperhomocysteinemia (HHcy), subclinical hypothyroidism, and high levels of high-sensitivity C-reactive protein (hs-CRP) have been considered risk factors for stroke [27]. These factors play a significant role in the pathogenesis of atherosclerosis by generating excessive reactive oxygen species and promoting the oxidation of low-density lipoproteins (LDLs) into atherogenic particles [28,29]. Diabetes and hypertension are the most serious comorbidities. It has been found that many epilepsy patients receiving AEDs exhibit multiple risk factors for stroke [26,30].

Lipid abnormalities

Lipid abnormalities play a significant role in the pathogenesis of atherosclerosis [31]. A range of AEDs, including enzyme-inducing AEDs (EI-AEDs), enzyme-inhibiting AEDs and non-enzyme-inducing AEDs (NEI-AEDs), have been reported to be differentially associated with abnormalities in lipid levels [32–34]. Patients taking EI-AEDs such as CBZ, PHT, and PB show higher levels of total cholesterol (TC), triglycerides (TGs), and LDL cholesterol (LDL-c) [35–37]; however, the available evidence about the effects of EI-AEDs on high-density lipoprotein cholesterol (HDL-c) is inconsistent [26,34,36]. Similarly, OXC, a new-generation, weak EI-AED, was reported to be associated with increased concentrations of TC, TGs, and LDL-c among adult epileptic patients [32,38] and to have a minor effect on serum lipids in children [39,40]. In contrast with EI-AEDs, enzyme-inhibiting AEDs and NEI-AEDs do not significantly affect lipid profiles. However, the effects of VPA, an enzyme-inhibiting AED, on lipid profiles remain unclear [36,37,41]. Most new-generation AEDs, including levetiracetam (LEV), LTG, and topiramate (TPM), are NEI-AEDs. With the exception of LEV, NEI-AEDs have been demonstrated to have no effect on lipid profiles [42,43]; LEV has been found to be associated with higher LDL-c levels in a recent study [32]. Therefore, EI-AEDs are most strongly associated with lipid abnormalities.

Weight gain, obesity, and IR

Weight gain, obesity, and IR have been shown to be linked with atherosclerosis [44]. Several cross-sectional and prospective studies have revealed that patients who have been treated with AEDs for prolonged periods are more likely to experience weight gain, obesity, and IR [45]. A considerable amount of data has shown that VPA, CBZ, PHT, gabapentin (GBP), vigabatrin (VGB), and pregabalin (PGB) have been associated with being overweight or obese [45–47]. In contrast, LTG and LEV have been reported to have no effects on weight [48,49], and decreased weight has been observed in patients receiving felbamate (FBM), TPM, and zonisamide (ZNS) [49,50]. Additionally, patients with refractory epilepsy have higher rates of overweight and obesity than do patients with drug-responsive epilepsy, and polytherapy has been shown to result in higher rates of overweight and obesity than monotherapy [51].

IR has been observed in some patients. It has been reported among patients with epilepsy receiving VPA and PHT [36,52]. In contrast, TPM has been found to improve glycemic control [53].

Hyperhomocysteinemia

HHcy has been demonstrated to be an independent risk factor for stroke [54]. The association between HHcy and AEDs has been widely studied, and numerous studies have found that patients exposed to OXC, PHT, PB, TPM, and PRM exhibit elevated levels of Hcy [26,32,55], whereas the effects of LTG on Hcy have been reported to be neutral [26,56]. Additionally, CBZ, VPA, and LEV have been shown to have inconsistent effects on Hcy [26,32,56–58]. The increased Hcy concentrations observed in patients receiving AEDs therapy have been proposed to be associated with the depletion of folate and vitamins B6 and B12, which are cofactors in the metabolism of Hcy [59].

Carotid-artery intima media thickness

Carotid-artery intima media thickness (CA-IMT) has been found to be an early marker of cerebral atherosclerosis [60]. Recently, many studies have reported an increased CA-IMT in epilepsy patients receiving AEDs therapy [26,60–62]. Furthermore, the observed increases in CA-IMT were positively and independently correlated with the duration of AEDs therapy [26,61]. Compared with control subjects, old-generation AEDs, including CBZ, PHT, and VPA, significantly increased CA-IMT in adult epilepsy patients [26,60]. However, the effects of these AEDs were inconsistent in children [57,61,62]. Thus far, the new-generation AEDs, such as LTG and OXC, have not been found to have an effect on CA-IMT in adults or children [26,39].

Others

Hyperuricemia has been suggested to be another important factor in the pathogenesis of atherosclerosis [63]. Elevated concentrations of uric acid have been found in patients receiving VPA [34]; such elevated levels may be caused by altered renal excretion of VPA [64]. However, CBZ and PHT have been shown to decrease serum levels of uric acid [65].

High concentrations of hs-CRP have been demonstrated to activate the extrinsic pathway of the coagulation system [66]. Long-term AED use may lead to higher levels of hs-CRP [60,67], which may have implications for atherosclerosis in epilepsy populations [60].

Hypothyroidism may be a risk factor for atherosclerosis through multiple mechanisms [68]. Subclinical hypothyroidism has been reported in patients receiving AEDs. It has been

shown that CBZ, PHT, PB, VPA, and OXC may lead to subclinical hypothyroidism [69–71].

The epileptic seizure

Current epidemiological studies have suggested that the increased risk of stroke that is observed in epilepsy patients is associated with the epileptic seizure itself. In a cohort study, Olesen et al. reported a higher risk of stroke in untreated epilepsy patients than in the general population [24]. Meanwhile, in another cohort study in Taiwan population, the risk of stroke was also shown to be higher in epilepsy patients without any vascular risk factors, such as hypertension, atrial fibrillation, cardiovascular disease (CAD), diabetes, or hyperlipidemia [4].

Moreover, among patients who have never received AEDs therapy, Hamed observed increased Hcy, thiobarbituric acid reactive substances, and CA-IMT, along with decreased levels of HDL-c and glutathione peroxidase, all of which increase vulnerability to subclinical atherosclerosis [34]. It has been proposed that recurrent epileptic seizures could contribute to the overproduction of reactive oxygen species and the oxidation of LDLs into atherogenic particles [28,29]. There is also an article that addressed mitochondrial DNA damage due to oxygen radicals that might cause epileptic disorders, which seemed to be a vicious circle [72]. Additionally, convulsions could worsen strokes by inducing acute hypertension and airway compromise. For example, generalized seizures often lead to an abrupt increase in mean arterial pressure, which may prompt an aneurysm to bleed again [73].

Therefore, epileptic seizures may play a role in the development of postepilepsy stroke; however, this hypothesis requires further study.

Lifestyle-related risk factors

Certain lifestyles may also increase the risk of stroke in epilepsy patients. Several studies have reported that epilepsy patients tended to adopt unhealthy lifestyles, such as smoking, physical inactivity, and certain unhealthy dietary choices [74–77], which have been demonstrated to be risk factors for stroke [78].

Current data have revealed a higher rate of cigarette smoking in the epilepsy population [74,75,77]. Compared with nonsmokers, cigarette smokers are approximately two times more likely to have a stroke during their lifetimes [79], and smoking has been demonstrated to be an important, modifiable and independent risk factor for the development of stroke in both sexes [80] and one of the significant contributing factors to stroke mortality [81]. Smoking can affect all arteries [82] and is considered to be a predictor of arterial stiffness [83].

An increased rate of physical inactivity has been observed among epilepsy patients [74,75,77]. It is well accepted that a lack of exercise is associated with an increased risk of stroke [84,85]. A multinational case–control study has further found physical inactivity to be the second most important risk factor for stroke [84].

Moreover, unhealthy dietary choices (such as fewer fruits and vegetables, more nondiet soda) are more commonly observed in epilepsy patients than in the general population [74], and an unhealthy diet is viewed as a lifestyle risk factor for stroke [84]. A study by Tikk et al. has also suggested an inverse association between a healthy diet and stroke risk [78].

Diabetes and hypertension

Diabetes and hypertension are two of the classical risk factors in postepilepsy stroke. In 2004, it was proposed that diabetes appeared more frequently in epilepsy [15]. Then, Tellez-Zenteno et al. proved that the prevalence of diabetes in epilepsy is higher than the general population [6]. And Seidenberg et al. hold the similar opinion [86]. In 2014, a population-based study further showed that, compared to the control, the prevalence of diabetes was significantly higher in epilepsy (24.8%; 95% CI 24.4–25.1) [14].

As to hypertension, most studies agreed that here were higher rates of hypertension in epilepsy patients, although Tellez-Zenteno suggested the same prevalence of hypertension in epilepsy and general population [6,19,86–88]. Early in 1993 and 1996, studies suggested a higher risk of hypertension in epilepsy patients [87,88]. In 2009, Seidenberg et al. also accepted this point of view [86].

So far, no research directly studied the reason for this phenomenon. We speculate that the side effects of AEDs, the influence of epileptic seizures, and the unhealthy lifestyles may contribute to the increased hypertension and diabetes in epilepsy patients.

We should emphasize that different risk factors are obviously interrelated with each other. For example, chronic use of AEDSs works as an important cofactor in the pathomechanism of epileptic disorder. And diabetes and hypertension can be serious comorbidities in patients receiving AEDs. A slight move in one part may affect the situation as a whole. Epilepsy patients should attach great importance to this issue.

Management

Numerous studies have shown that these increased risks of stroke and increased mortality from stroke in the epilepsy population are associated with the use of AEDs, the epileptic seizures themselves, and the lifestyles of epilepsy patients. Therefore, to prevent the development of postepilepsy stroke, it is important to monitor patients' risk factors for stroke, choose the appropriate AEDs for each individual patient, and help each patient to establish a healthy lifestyle.

Monitoring risk factors, statins, and vitamins

Monitoring risk factors

It has been demonstrated that epilepsy patients treated with AEDs or not exhibit increased risk factors for stroke, including lipid abnormalities, weight gain, obesity, IR, HHcy, hyperuricemia, increased CA-IMT, and other abnormalities [34,45]. Moreover, it has been reported that the coexistence of multiple risk factors in individual patients is common [27]. Therefore, it is essential to monitor stroke risk factors, such as blood pressure, TC levels, TG levels, LDL-c levels, HDL-c levels, weight, glucose, insulin, Hcy, uric acid levels, and thyroid hormone levels. Additionally, it has been suggested that noninvasive ultrasonography be used to examine the CA-IMT

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regularly. Once any of the risk factors is found in the epilepsy patients, we strongly suggest that the appropriate medication be given as primary prophylaxis of stroke.

HHcy result from decreased methylenetetrahydrofolate reductase (MTHFR) enzyme activity caused by polymorphisms in the MTHFR gene and/or inadequate folate intake, induced by old-generation AEDs. In 2004, it was found that the epilepsy patients treated with EI-AEDs had significantly more frequent C677T/AC1298 diplotype than controls, and concomitant low folate levels HHcy [89]. Belcastro et al. got the similar results and further proved that folate therapy could decrease Hcy and folate to normal ranges in all patients [90]. Thus, it is suggested that both C677T and A1298C MTHFR polymorphisms should be examined when assessing genetic risk factors of HHcy in epilepsy. And folate therapy should be given to ensure physiological Hcy levels in epilepsy.

The recommendation to monitor the metabolic alterations routinely along longer time seems to be difficult to execute. The following is our suggestion. For obese patients (body mass index > 25), and patients with high-fat salt diet and other risk factors, they may check blood pressure, blood sugar, blood lipids, and other indicators once every 3–6 months. For patients without those risk factors, they may check these indicators every 6–12 months. For patients with diabetes or hypertension, a home blood pressure kit or a home use glucometer are needed to monitor blood pressure or blood sugar regularly (at least once a week).

Statins in epilepsy

It is worth noting the role of statins in epilepsy. Introduced as 3-hydroxymethylglutaryl-coenzyme-A reductase inhibitors, statins are used to lower lipid levels, and they also have vasodilatory, antithrombotic, anti-inflammatory, antioxidant, and neuroprotective effects [91,92]. Statins have been identified as one of the most effective therapies for stabilizing vulnerable atherosclerotic plaques [93]. Moreover, considerable data have shown that statins, especially at high doses, could retard, reduce, and even reverse plaque progression [94,95]. Additionally, evidence from experimental and clinical studies and meta-analyses has suggested that treatment with statins could improve stroke outcomes [96,97]. Importantly, it was found that statins could potentially prevent epilepsy [98,99]. Therefore, statins may be a favorable choice for epilepsy patients with lipid abnormalities.

Vitamins in epilepsy

Vitamins and multivitamins have been demonstrated to have antioxidant and anti-inflammatory effects. They have been shown to decrease lipid and Hcy levels, and they thus play an important role in athero protection [100]. A prospective monocenter study in a large population found that AEDs interact with folate and vitamin B12 serum levels [55]. The reduction of folate or vitamin B12 serum levels could be noticed in patients taken the commonly used AEDs, which was a risk factor for HHcy [55]. Additionally, nutrient deficiencies, including deficiencies in vitamins E and B-6 and folate, have been reported among children with intractable epilepsy [101]. Based on the lipid abnormalities, HHcy, and vitamin deficiencies that are observed in epilepsy, it has been considered important to supply multivitamins (include folic acid, vitamin B12, vitamin B6, vitamin C, vitamin E, and β-carotene) routinely to patients of all ages [102,103]. However, some researchers have found no benefits and sometimes even harmful effects from supplementation with antioxidants (vitamins C, E, and β-carotene) in atherosclerosis [104,105]. Therefore, low doses of folic acid (0.4 mg) and B vitamins (e.g. B2, B6, B12) have been recommended to treat or prevent the consequences of deficiencies in folate and other vitamins in patients receiving AEDs [103], which is just appropriate to restore vitamin and homocysteine levels [55].

Changing unhealthy lifestyles

Higher rates of cigarette smoking, physical inactivity, and unhealthy dietary choices have been reported in epilepsy patients [74–77], which increase the risk of stroke [106]. Therefore, epilepsy patients should be advised to change their lifestyles.

Firstly, smoking cessation is strongly recommended for epilepsy patients. Smoking has been demonstrated to be an important and modifiable risk factor for stroke [80]; smoking cessation can reduce the risk of stroke [107,108] and mortality from stroke [109]. Meanwhile, it has been recognized that nicotine administration can lead to epileptic seizures [110]. People exposed to acute secondhand smoke and chronic active smokers have higher risks of seizures [111].

Secondly, accumulating evidence indicates that regular exercise is a healthy lifestyle choice that could prevent hypertension and features of metabolic syndromes, such as obesity, higher fasting glucose and TG levels, and low concentrations of HDL [112]. Furthermore, regular exercise can decrease the risk of stroke and of the recurrence of stroke [113] and can improve the prognosis of stroke [114]. In an investigation of 240 patients with active epilepsy, 36% of the patients believed that regular exercise improved seizure control [115]. It has also been demonstrated that recommended levels of exercise can decrease mortality from stroke among epilepsy patients [74]. Howard et al. have demonstrated that epilepsy patients can participate in most forms of physical activity, including some contact sports [116]. It has also been suggested that epilepsy patients should start exercise programs slowly and gradually increase their levels of physical activity [74]. Thirdly, a healthy diet is recommended. It has been found that epilepsy patients make unhealthy dietary choices compared with the general population [74]. Some studies have shown that a healthy diet (rich in fruits, vegetables, legumes, whole grains, fish, and nuts; low in fat and sugar) is associated with a decreased risk of stroke [117,118] or with prevention of stroke [119]. Moreover, a decreased mortality from stroke has been reported among patients with a healthy diet [120]. Besides, low glycemic index treatment (LGIT) has been demonstrated to be effective for seizure control in patients with drug-resistant epilepsy [121]. LGIT is characterized by low carbohydrate intake, with a glycemic index of <50 relative to glucose, and decreased fat intake [122], and it can lower the postprandial plasma glucose and insulin profiles in diabetics [123]. Therefore, a low-carbohydrate diet may improve seizure control, and LGIT is recommended for epilepsy patients with IR or diabetes.

Choice of AEDs

Considering the side effects of AEDs, treatment with NEI-AEDs (such as LTG, TPM, and LEV) is recommended for epilepsy patients with lipid abnormalities. TPM, ZNS, FBM, LTG, or LEV is recommended for obese epilepsy patients. TPM has been found to be beneficial for diabetic patients in terms of improving glycemic control [53]. Therefore, TPM should be the first choice of AEDs for patients with diabetes or IR, whereas VPA and PHT should be avoided in these patients. However, cognitive dysfunction was frequently observed in patients receiving topiramate, especially with regard to speech. Therefore, the selection of topiramate should be deliberate, especially for children [124]. LTG should be given to patients with HHcy, and CBZ, OXC, VPA, PHT, PB, LEV, and PRM should be avoided in such patients. CBZ and PHT should be chosen for patients with hyperuricemia, and VPA should be avoided in these patients. In addition, treatment of CBZ, PHT, PB, VPA, and OXC should be avoided in patients with hypothyroidism.

Conclusion

The collective evidence suggests that epilepsy patients face an increased risk of stroke and increased mortality from stroke compared with the general population. This increased risk of stroke in epilepsy patients may be associated with AEDs use, epileptic seizures themselves, and patient lifestyles. Therefore, in clinical practice, we should monitor epilepsy patients' stroke risk factors, such as serum lipids, glucose, and Hcy, and prescribe appropriate medications. Moreover, we should help these patients to establish a healthy lifestyle, including smoking cessation, appropriate exercise, and healthy dietary choices, and we should choose appropriate AEDs for epilepsy patients with metabolic syndromes.

Expert commentary

Epilepsy and stroke are two of the most common neurological disorders with high mortality and disability rates. However, the stroke after epilepsy (or postepilepsy stroke) does not get enough attention in clinical practice. In recent years, different kinds of epidemiological studies have demonstrated a much higher risk of stroke, an increased mortality from stroke in epilepsy patients than the general population. The aim of this review is to emphasize the importance of postepilepsy stroke in clinical practice, to help physicians comprehensively understand the relationship between epilepsy and postepilepsy stroke, to provide general and specifically targeted strategies to minimize the risk of stroke in this population. There are some limitations to this review: with respect to the etiology of epilepsy, onset age, gender and the type of stroke, discussion about the association between mortality and the etiology, the association between age/gender/the type of stroke and postepilepsy stroke are not thorough enough due to the limited information. Also, the CADASIL patients, arteriovenous malformation, and mitochondrial disease are closely associated with epilepsy and stroke (but not postepilepsy stroke) and worth to be reviewed in a new article. We recommend the establishment of a case network to collect more data. This would be beneficial to the large-scale studies and could improve clinical understanding about the postepilepsy stroke.

Five-year view

Although some studies focus on it from many aspects (epidemiology, AEDs, age, gender, lifestyle, etc.), unfortunately, postepilepsy stroke did not get enough attention in the clinical practice. Only a few literature relevant to postepilepsy stroke are available while overwhelming amount of data are associated with the epilepsy after stroke. Therefore, it is urgent for the neurologist to comprehensively study postepilepsy stroke. On the other side, the knowledge about the increased risk of stroke in epilepsy should be included in the patient education. Over the next five years, many advances will likely involve the mechanism of postepilepsy stroke. With continued progress in the networks, we can establish a case network to collect more data to help us understand more of the complex relationship between epilepsy and future stroke to promote a more comprehensive patient evaluation that includes seizure treatments and stroke prevention.

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Key issues

- The relationship between epilepsy and stroke is complicated. Stroke has been viewed as one of the most important causes of epilepsy. However, the stroke after epilepsy (or postepilepsy stroke) does not get enough attention in clinical practice.
- Various epidemiological studies showed that there was a higher risk of stroke and increased mortality from stroke in epilepsy patients. The increased risk of stroke is associated with the type, the dose, the duration of antiepileptic drug (AED) exposure. Combination of AEDs may increase the risk of stroke.
- The causes of postepilepsy stroke remain unclear. It has been proposed that the side effects of AEDs, epileptic seizures themselves, or the lifestyles of epilepsy patients may contribute to the development of postepilepsy stroke.
- It is essential to monitor stroke risk factors, such as blood pressure, total cholesterol levels, lamotrigine levels, low-density lipoprotein-cholesterol levels, high-density lipoprotein cholesterol levels, weight, glucose, insulin, homocysteinemia, uric acid levels, and thyroid hormone levels in epilepsy patients. Once any of the risk factors is found in the epilepsy patients, it is strongly suggested that the appropriate medication be given as primary prophylaxis of stroke.
- Considering the positive effects of healthy dietary choices, regular exercise, and smoking cessation on the risk of stroke, epilepsy patients should be advised to change their lifestyles.
- Appropriate AEDs should be given to the epilepsy patients with metabolic syndromes. For example, non-enzyme-inducing-AEDs are recommended for epilepsy patients with lipid abnormalities; valproic acid, carbamazepine, phenytoin, gabapentin, vigabatrin, and pregabalin should be avoided in obese epilepsy patients.

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