

# The causes of new-onset epilepsy and seizures in the elderly

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**Abstract:** With increasing age, the prevalence and incidence of epilepsy and seizures increases correspondingly. New-onset epilepsy in elderly people often has underlying etiology, including cerebrovascular diseases, primary neuron degenerative disorders, intracerebral tumors, and traumatic head injury. In addition, an acute symptomatic seizure cannot be called epilepsy, which manifests usually as a common symptom secondary to metabolic or toxicity factors in older people. In this review, we have mainly focused on the causes of new-onset epilepsy and seizures in elderly people. This knowledge will certainly help us to understand the reasons for high incidences of epilepsy and seizures in elderly people. We look forward to controlling epileptic seizures via the treatment of primary diseases in the future.

**Keywords:** epilepsy, seizures, causes, elderly

## Introduction

Epilepsy is one of the most common diseases of the nervous system in the elderly, second to dementia and stroke.<sup>1</sup> Geriatric epilepsy includes pre-elderly (<60 years old) epilepsy continuing to old age stage, and new-onset epilepsy in the elderly. Epilepsy, especially late-onset epilepsy, significantly impacts the quality of life of older people and increases the health care resource burden on society.<sup>2</sup>

Old age stage is a peak period for developing epilepsy and seizures.<sup>3</sup> The incidence of epilepsy and seizures is higher in the elderly ( $\geq 60$  years old) than in other age groups.<sup>4,5</sup> It has been estimated that the annual incidence is 85 per 100,000 for people aged 65–69 years, 159 per 100,000 for people aged over 80 years, and 80.8 per 100,000 people over all age groups.<sup>6</sup> A recent epidemiological study shows that the average annual incidence of epilepsy in the elderly, aged 65 years and older, is up to 240 per 100,000.<sup>7</sup> Nearly 25% of new-onset epilepsy occurs in the elderly.<sup>8</sup> Some scholars predict that the elderly will account for half of all new-onset epilepsy people by 2020.<sup>9</sup>

The existence of some special causes may contribute to the high incidence of epilepsy in the elderly. It is reported that an underlying etiology can be found in nearly 50% of elderly patients.<sup>10</sup> In 2010, the International League Against Epilepsy (ILAE) Commission for Classification of Epilepsy divided epilepsies into three categories (genetic, structural/metabolic, unknown cause) according to the etiologies of epilepsy.<sup>11</sup> This classification applies to all age groups, including the elderly. Specific causes are correlated with the age groups; different age groups tend to have different causes of epilepsy.<sup>3</sup> Younger patients with epilepsy often show a genetic cause. However, new-onset epilepsy in the elderly is mainly the consequence of accumulated injuries to the brain and other secondary factors.<sup>12,13</sup> The most common acquired etiologies

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of new-onset epilepsy and seizures in the elderly include cerebrovascular diseases, primary neuron degenerative disorders associated with cognitive impairment, intracerebral tumors, and traumatic head injury.<sup>9,14</sup> We have summarized the percentage of each cause of new-onset epilepsy in the elderly in Table S1. Identification of the causes in the elderly with new-onset epilepsy or seizures may contribute to seizure control via the treatment of primary diseases.

In this review, we have focused on analyzing the causes of new-onset epilepsy in elderly people. In addition, we have also mentioned potential unknown causes and causes of acute symptomatic seizures. In the last part of our review, we have summarized the common causes of status epilepticus (SE), which is not uncommon in the elderly.

## Acquired causes of new-onset epilepsy in the elderly

### Cerebrovascular diseases

Stroke and other cerebrovascular diseases are the most important risk factors for new-onset epilepsy in the elderly, which account for 30%–50% in all identified causes.<sup>10,15–17</sup> In general, epilepsy can occur at the time or after stroke, or can be an early clinical manifestation of cerebrovascular diseases. Studies have reported that the risk of developing epilepsy in the first year after a stroke increases by 20 times.<sup>15</sup> Table 1 shows the studies in which the risk of developing epilepsy within the first year has been described regarding cerebrovascular diseases.<sup>18–24</sup> The number of lesions, and the size of the stroke site are closely linked to the probability of the occurrence of epilepsy. A 12-year follow-up study shows that visual neglect, dysphasia, and stroke subtype (particularly total anterior circulation infarcts), are predictors of poststroke epilepsy.<sup>25</sup> Epilepsy is mainly due to mechanical stimulation of a stroke lesion, nerve cell degeneration, gliosis around the lesion, and glial scar formation. Ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage are common risk factors of poststroke epilepsy.<sup>26,27</sup>

**Table 1** Studies in which the risk of developing epilepsy within the first year has been described regarding cerebrovascular diseases

Studies	Patients with poststroke epilepsy at 1 year
Bladin et al <sup>18</sup>	3.8% (9 months)
Burn et al <sup>19</sup>	4.2%
So et al <sup>20</sup>	3.0%
Lamy et al <sup>21</sup>	3.1%
Lossius et al <sup>22</sup>	2.5%
Roivainen et al <sup>23</sup>	6.9%
Hsu et al <sup>24</sup>	15%

### Ischemic stroke

Several studies have reported that seizures often originate from regions that are only partly destroyed, not from completely infarcted areas.<sup>28–30</sup> Hemorrhagic transformation of ischemic stroke is a risk factor for epilepsy,<sup>31</sup> which might be related to the blood–brain barrier disruption.<sup>32</sup>

Thrombotic stroke is common in the elderly because of the coexistence of cardiovascular diseases. One study has shown that patients with suspected cardio embolic etiology have almost two times the risk of developing epilepsy compared with those who have vessel thrombosis, because the thrombosis from the heart is more likely to lead the thrombotic stroke.<sup>27</sup>

Genetic factors account for ~30% of the causes in patients with epilepsy.<sup>33</sup> In patients with ischemic stroke, genetic factors also contribute to the consequent epileptogenesis. Allele A of the rs671 polymorphism in a gene encoding mitochondrial aldehyde dehydrogenase 2 is associated with poststroke epilepsy.<sup>34</sup> A CD40-1C/T polymorphism is associated with poststroke epilepsy susceptibility.<sup>35</sup> Other genes like 12SNPs and a functional connectivity of many genes at the transcriptomics level have been found to exist in the context of ischaemic stroke. Further research is required to determine whether these genes exist in patients with poststroke epilepsy.<sup>36</sup>

In addition, lifestyle factors (eg, smoking, alcohol use), acute metabolic disturbances (eg, acid-base imbalance, electrolyte imbalance, hyperglycemia), non-central nervous system (CNS) morbidities (eg, diabetes 1 or 2, dyslipidemia, renal insufficiency, hypertension, coronary heart diseases or myocardial infarction, peripheral infections), CNS morbidities (eg, early seizures, SE within 2 weeks poststroke, depression or use of antidepressants, dementia), and pharmacotherapy (eg, antiepileptic drugs, noradrenergic blockers, noradrenergic agonists, benzodiazepines, voltage-sensitive calcium-channel blockers, statins) are associated with poststroke epileptogenesis in patients with ischemic stroke.<sup>36</sup>

### Hemorrhagic stroke

Patients with hemorrhagic stroke, especially lesions involving the cerebral cortex,<sup>27</sup> are more susceptible to develop epilepsy after stroke. Furthermore, lesions with venous injury are more likely to present as epilepsy because venous injury may influence the cortex, for example, intracranial bleeding accompanies cerebral venous thrombosis and shows tendency to secondary epilepsy compared to basal ganglia hemorrhage.<sup>27</sup> Moreover, subarachnoid hemorrhage is more

likely to cause epilepsies than intracranial hemorrhage, which is related to secondary bleeding.<sup>27</sup>

#### Small vessel and microvascular diseases

Besides large vessel diseases, small vessel and microvascular diseases of the CNS are causes of epilepsy. It is reported that risk factors of cerebrovascular diseases, such as high blood pressure, high cholesterol, and coronary and peripheral arterial disease, are associated with epilepsy, even in the absence of stroke, which is confirmed by radiographic evidence.<sup>9</sup> Therefore, it is reasonable to suspect that microvascular diseases contribute to geriatric epilepsy. Microvascular diseases such as leukoaraiosis and lacunar infarcts, especially when accompanied with impaired cognition, have a greater risk for poststroke epilepsy than patients without cognitive impairment.<sup>37</sup> Cerebral amyloid angiopathy is associated with small vessel diseases, including white matter hyperintensities and cerebral microbleeds; some publications report that epilepsy is primarily related to the presence of lobar hemorrhages, which result from cerebral amyloid angiopathy in the elderly.<sup>38</sup>

#### Other cerebrovascular diseases

In addition to these common cerebrovascular diseases, other cerebrovascular diseases including cerebral vein and sinus thromboses, or vascular malformations are risk factors for epilepsy.<sup>39</sup> For patients accompanied by cerebral vein thrombosis, blood deposits in the capillary and venous systems, thereby enabling local brain tissue swelling, nerve cell degeneration, necrosis, and even venous infarction or hemorrhage, eventually leading to the occurrence of epilepsy. Vascular malformations and cavernomas can cause epilepsy, but these are not common in the elderly or in younger patients without bleeding.

#### Epilepsy and subsequent development of cerebrovascular diseases

In fact, there is a mutual link between epilepsy and cerebral vascular diseases. In some patients with generalized seizures, mean arterial pressure increases rapidly, leading to aneurysm rupture, and rebleeding, causing seizures.<sup>25</sup> Cleary et al have shown that the onset of seizures in later life is associated with a striking increase in the risk of stroke, with a threefold risk of subsequent stroke.<sup>40</sup> Patients presenting with late-onset epilepsy have a greater presence of myocardial infarction, peripheral artery disease, hypertension/left ventricle hypertrophy, high cholesterol level, silent ischemic lesion, and leukoaraiosis.<sup>41</sup> These factors may increase the incidence

of subsequent development of cerebrovascular diseases. Therefore, elderly patients with new-onset epilepsy should be assessed for the risk factors of cerebrovascular diseases, and be given interventions for these risk factors in order to prevent the occurrence of cerebrovascular diseases.

Hepatic enzyme-inducing antiepileptic drugs increase serum lipid levels and other atherogenic markers via the induction of cytochrome P450 and may therefore increase the risk of vascular events. A population-based cohort study conducted by Renoux et al revealed that there is a slight increase in the risk of myocardial infarction with prolonged use of enzyme inducers antiepileptic drugs (>24 months), but not a clear increased risk of stroke.<sup>42</sup> Therefore, further studies should be conducted to confirm whether antiepileptic drugs increase the risk of stroke.

### Primary neurodegenerative disorder associated with cognitive impairment

Alzheimer's disease (AD) and other neurodegenerative conditions are risk factors of epilepsy.<sup>43–45</sup> It is reported that patients with all types of dementias are at a fivefold to tenfold increased risk of epilepsy compared to an age-matched population without dementia.<sup>46</sup> Primary neurodegenerative disorders account for ~10%–20% of all identified causes in older people.<sup>47</sup> However, the incidence and prevalence of epilepsy in patients with degenerative dementias might be underestimated due to several factors. Firstly, it is difficult to collect the clinical history from caregivers of dementia. Secondly, it is sometimes difficult to recognize the manifestations of seizures in dementia patients because of the many abnormal behaviors that demented patients often manifest.

During primary neurodegenerative disorders, several factors contribute to epilepsy, including the type of neurodegenerative disorder, the severity and process of dementia, epileptiform discharges in patients with dementia, and race.

First, AD is responsible for the largest proportion of dementia patients with epilepsy. The risk of developing seizures and epilepsy for patients with AD is 3–87 times higher than the same-aged general population.<sup>48</sup> Non-AD dementias increase the risk of partial seizures elevenfold and the risk of generalized seizures sevenfold.<sup>49</sup> Of all non-AD dementias, Creutzfeldt–Jakob disease has a higher risk to present epilepsy, the incidence of which is up to 20%.<sup>50</sup> However, mixed dementia, vascular dementia, and dementia with Lewy body may account for a very small percentage of epilepsy.<sup>15</sup> Unfortunately, there are no data regarding the prevalence of epileptic disorders in vascular dementia,

**Table 2** Different dementias related to epilepsy

AD	3–87 times higher than the same-age general population
Non-AD dementias	Increase the risk of partial seizures elevenfold and the risk of generalized seizures sevenfold
Creutzfeldt–Jakob disease	The incidence is up to 20%

**Note:** There are no specific data about other dementias.

**Abbreviation:** AD, Alzheimer's disease.

mixed dementia, Lewy body disease, and frontotemporal dementia. Table 2 explains the risk of different dementias in relation to epilepsy.

Second, the severity and process of dementia are related to the possibility of developing epilepsy. The severity of this disease may increase the incidence of seizures.<sup>51</sup> Seizures can occur in 1.5%–16% of patients with mild dementia, compared to 9%–64% of patients with severe dementia.<sup>48</sup> Secondary epilepsy can occur at any stage of neurodegenerative diseases, but it commonly develops after years of this progressive disorder.<sup>52</sup> The average time of suffering from epilepsy after the onset of dementia is 6.8 years.<sup>53,54</sup> The risk of epilepsy increased by 11% and 26% at 10 and 15 years, respectively, in a follow-up study of AD patients.<sup>55</sup> This may be associated with increasing age and increasing severity of the neurodegenerative process.

Third, an epileptiform discharge on electroencephalogram is strongly predictive of seizures in AD patients.<sup>56</sup> Therefore, the examination of electroencephalogram can be used as an important predictor of seizures for patients with AD.

Fourth, race is possibly related to the incidence of epilepsy in patients with dementia. Limited research has shown that African-American ethnicity is a risk factor for developing seizures in AD;<sup>56</sup> however, this result may be related to the small sample size in the paper. Sherzai et al<sup>44</sup> and Scarmeas et al<sup>52</sup> did not find this distinction in their studies. Therefore, evidence as to whether race contributes to epilepsy in patients with dementia is inconsistent. Large-scale clinical trials are needed to confirm this relationship.

Specific epileptogenic mechanism is still uncertain in patients with neurodegeneration; there are several reasons that might be associated with secondary epilepsy in dementia, including  $\beta$ -amyloid deposition, neuronal loss and gliosis, chemical changes, antidementia drugs, and comorbidities.<sup>46,48,57–60</sup>  $\beta$ -Amyloid deposition is a pivotal pathologic change in AD, which is also an important epileptogenic mechanism for patients with AD.  $\beta$ -Amyloid is related to synaptic activity and serves as a potent regulator of synaptic transmission, causing presynaptic facilitation at relatively low

concentrations and postsynaptic depression at higher levels, thereby producing epileptiform activity.<sup>61</sup> This fact is confirmed in an animal experiment on transgenic mice models of AD that showed that high levels of  $\beta$ -amyloid can induce epileptiform activity and seizures.<sup>57</sup> The possible selective loss of the inhibitory neurons might be another mechanism of epileptic seizures in AD patients.<sup>54</sup> Moreover, chemical changes in AD patients may induce seizures; these chemical factors include alterations in acetylcholine, dopamine, gamma-aminobutyric acid and other neurotransmitters, or changes in cellular excitotoxicity and sodium and calcium channel functions.<sup>53</sup> In addition, dementia-associated drug use is an important risk factor for developing epilepsy. Studies have shown that a history of antipsychotic use is a risk factor for new-onset epilepsy in AD.<sup>58</sup> Evidence regarding whether antidementia drugs can provoke seizures is limited. It has been shown in an animal study that memantine has proconvulsive and anticonvulsive properties.<sup>62</sup> In a case report, Donepezil was found to provoke seizures.<sup>63</sup> However, large observational studies are lacking.

Lastly, dementia-associated comorbidities are also risk factors for developing epilepsy. It is reported that hypertension and diabetes may be potential factors for developing epilepsy in AD.<sup>59,60</sup>

## Trauma

Head trauma is a common cause of intractable epilepsy, accounting for 10%–20% of symptomatic epilepsy in the general population and 5% of all epilepsy.<sup>64</sup> One study in children and young adults has shown that the risk of post-traumatic epilepsy is the highest in the first year, although it remains a high risk in the next 10 years or longer.<sup>65</sup> This phenomenon may also be seen in the elderly. Traumatic brain injury has been proved as a cause of epilepsy in animal models; in fluid-percussion and controlled cortical impact models, spontaneous electrographic seizures have been recorded.<sup>64</sup> Unfortunately, molecular and cellular changes of predicting epileptogenesis are still unclear.

Older people are more likely to fall, which may result in serious consequences such as head injury; therefore, the risk of post-traumatic epilepsy in people aged 65 years or older becomes higher. Risk factors associated with post-traumatic epilepsy include penetrating injuries, injury severity, biparietal or multiple contusions, intracranial hemorrhage, frontal or temporal location of the lesion, skull fracture, subdural hematoma, brain midline shift greater than 5 mm, amnesia for more than 1 day, loss of consciousness for more than 1 day, prolonged length of post-traumatic amnesia, multiple intracranial procedures, and the occurrence of early

post-traumatic seizures.<sup>64,66,67</sup> In addition, one prospective study has found that ApoE4 allele is related to the risk of late post-traumatic epilepsy.<sup>68</sup>

## Tumors

Brain tumor is a common cause of epilepsy second only to cerebrovascular disease in the elderly, accounting for nearly 10%–30% in all causes of geriatric epilepsy.<sup>16,69</sup> Epilepsy is a common manifestation in patients with brain tumors. Seizures are the onset symptom in 20%–40% of patients with brain tumor; 20%–45% of patients will present with epileptic seizures during the course of the disease.<sup>70</sup> Epileptic seizures caused by brain tumors may have the serious consequence of increasing mortality in the elderly.<sup>69</sup>

In the elderly, both primary tumors and brain metastases contribute to epilepsy. Common primary tumors associated with epilepsy include primary CNS lymphoma, meningioma, anaplastic ependymoma, and anaplastic astrocytoma.<sup>69</sup> Brain metastases often originate in the lungs, bladder, pancreas, esophagus, liver, breast, uterus, and colon.<sup>69</sup> Gliomas, meningiomas, and brain metastases are the most common brain tumors leading to seizures.<sup>71</sup> Individuals with primary tumors are more prone to develop seizures than those with secondary tumors. Patients with poorly differentiated tumors are more likely to develop seizures compared with those with well-differentiated tumors. Patients with low-grade tumors such as astrocytoma, oligodendroglioma, and mixed astrocytome I and II have a higher risk of developing epilepsy.<sup>70</sup>

The localization of tumors is also a common factor for developing epilepsy, rating after the types of tumors. Generally, tumors located in the temporal lobes, frontal lobes, and parietal lobes are more likely to cause seizures and epilepsy compared to tumors located in the medullary.<sup>27</sup>

## Potential unknown causes of new-onset epilepsy in the elderly

Although some of new-onset epilepsies in the elderly show identified etiology, one-third to one-half of geriatric epilepsies still have undetected causes, to date, despite the current advances in technology.<sup>10</sup>

Paraneoplastic limbic encephalitis and posterior reversible leukoencephalopathy syndrome are probably the most rare of the unknown causes of new-onset epilepsy in the elderly. Therefore, these rare factors should be taken into account when no identified causes can explain the reason for geriatric epilepsy.

Immune factors may be potential causes in patients with undetected causes. A recent study conducted in the

US of adult patients (most of whom could be considered elderly) in several intensive care units, highlights the immune origin of the novo new-onset refractory SE. In this case, immunomodulatory treatment is more effective than antiepileptic drugs.<sup>72</sup>

## Causes of acute symptomatic seizures

An acute symptomatic seizure is defined as the first seizure attack in people without epilepsy, occurring in close temporal relationship with an acute CNS insult, including metabolic, toxic, structural, infectious, and inflammation;<sup>73</sup> it differs from provocative seizure which occurs in people with epilepsy. Sleep deprivation, alcohol consumption, and feeling stressed are the most common factors of provocative seizure.<sup>74</sup>

Strictly speaking, acute symptomatic seizures cannot be diagnosed as epilepsy, however, acute symptomatic seizure is a common symptom in older adults, which increases the risk of developing epilepsy. The incidence of acute seizures in patients older than 60 years is ~100 per 100,000 and increases with each decade of advancing age.<sup>75,76</sup> Epilepsy persists in one-third of these patients with acute symptomatic seizures.<sup>77</sup> A study has shown that acute symptomatic seizures are the most common risk factors of SE and/or cluster seizures in the elderly, which is a neurologic emergency;<sup>78</sup> this phenomenon increases the risk of neurologic emergency for the elderly. Therefore, it is necessary for us to analysis the causes of acute symptomatic seizures in old adults.

Literature has indicated that cerebrovascular diseases, traumatic brain injury, neoplasm, CNS infection, and drug withdrawal are the major causes of acute symptomatic seizure.<sup>8</sup> We have explained the different etiologies of acute symptomatic seizures in Table 3.

Stroke is the most common cause of acute symptomatic seizures, which account for nearly half of acute symptomatic seizures.<sup>79</sup> Seizures which are present within 1 week of cerebrovascular disease are attributed to acute symptomatic seizures. Hemorrhage, lobar location, and anterior hemisphere location are related to a higher incidence of early seizures.<sup>20,80</sup> In the acute phase of stroke, epileptic discharges are induced by ischemia, hypoxia cerebral edema, or direct stimulation of injured neurons. In addition, seizure threshold can be reduced by the merger of dehydration, electrolyte imbalance, or infection in the acute phase. These reactions become pathogenic factors and contribute to acute symptomatic seizures. Within 15 days of a transient ischemic attack or a lacunar infarct, ~1%–2% of patients experience a seizure.<sup>81</sup> Seizures usually occur within the first 48 hours of ischemic stroke and within hours of subarachnoid hemorrhage.<sup>81</sup>

**Table 3** Different etiologies of acute symptomatic seizures**Cerebrovascular disease****Traumatic brain injury****Neoplasm****Central nervous system infection**

**Drugs** antibiotics, endocrine drugs, local anesthetics/anti-arrhythmia agents, psychotropic drugs, stimulant drugs, anesthetics, excessive anticonvulsants

**Illicit drugs** cocaine, crack, normeperidine, meperidine, methaqualone

**Prescription drugs withdrawal** barbiturates, benzodiazepines

**Internal medicine diseases** fever, hypoglycemia, electrolyte imbalance, water intoxication, pneumonia with or without respiratory failure, severe myxedema, liver failure, renal failure

**Lifestyle-associated factors** alcohol and alcohol withdrawal

Traumatic brain injury and neoplasm account for nearly 10% and 9% of symptomatic seizures, respectively.<sup>75</sup> Epileptic discharges may be caused by cerebral edema or the irritability of neoplasm. In addition, subdural hematoma and post-traumatic hemorrhage are associated with seizures in patients who have experienced traumatic brain injury.<sup>8</sup>

The elderly, especially people who have underlying diseases with lower immunity, are prone to CNS infections caused by viruses, bacteria, fungi, and parasites. CNS infection is another important risk factor of acute symptomatic seizures, which accounts for nearly 2% of symptomatic seizures.<sup>75</sup> CNS infection, especially affecting the temporal lobe, is a risk factor of SE, and it is more refractory,<sup>82</sup> so it is one of the causes that we must emphasize in the elderly, with those in developing countries more easily affected by it. As health conditions are poor in developing countries, CNS infection is more common in developing countries than in developed countries.<sup>83,84</sup>

Prescription drug use and drug withdrawal are important risk factors of acute symptomatic seizures in the elderly. Drugs and drug withdrawal account for up to 10% of acute symptomatic seizures in the elderly.<sup>8</sup> Common drugs that can cause seizures include antibiotics, endocrine drugs, local anesthetics/anti-arrhythmia agents, psychotropic drugs, stimulant drugs, anesthetics, and excessive anticonvulsants.<sup>85,86</sup> In addition, drug withdrawal is also sometimes associated with acute symptomatic seizures. For example, the withdrawal of barbiturates and benzodiazepines can lead to acute symptomatic seizures.<sup>86</sup> Moreover, large doses of medication, parenteral administration, and comorbidity are risk factors of acute symptomatic seizures related to drugs.<sup>15</sup> The elderly who are long-term hospitalized or have serious illness are more prone to experience drug-related seizures.<sup>15</sup> In addition, smoking may affect the distribution of theophylline; therefore, smoking patients are particularly prone to have generalized seizures when theophylline is prescribed.<sup>15</sup>

In addition, a number of internal medicine diseases contribute to 10%–15% of acute symptomatic seizures,<sup>87</sup>

including fever, hypoglycemia, electrolyte imbalance, water intoxication, pneumonia with or without respiratory failure, severe myxedema, liver failure, and renal failure; however, uremia, liver failure, hypoglycemia, hyponatremia, and hypoxia are the most common internal medicine disease causes.<sup>15</sup> These metabolic and toxicity factors may reduce seizure threshold, inducing acute symptomatic seizures, with these factors removed, seizures may no longer occur. Electrolyte imbalance, renal failure, and hypoglycemia or hyponatremia, are the most common internal medicine conditions in elderly people in our clinical work.

Electrolyte imbalance is a common factor associated with acute symptomatic seizures in the elderly. Elderly people with poor nutrition, and poor function of the lungs and kidneys are prone to be electrolyte imbalance, thus, it is a risk factor of acute symptomatic seizures, which should not be ignored. The concentration of ions across cell membranes induces abnormal discharge of neurons, thus causing seizures. Seizures may be the only symptom of electrolyte imbalances, which are commonly seen in people with sodium disorders, hypocalcemia (<5.0 mg/dL), and hypomagnesemia (<0.8 mg/dL).<sup>88,89</sup> The more rapid the disturbance develops the more likely it is to induce seizures,<sup>90</sup> especially when a rapid decrease of serum sodium occurs.<sup>91</sup> It is recommended that sodium concentration be reduced at a rate below 0.5 mmol/L/h to prevent seizures in patients with hyponatremia.<sup>92</sup>

Acute symptomatic seizure is one of the clinical manifestations of uremic encephalopathy, which is currently considered to be associated with a variety of factors, including toxin metabolites, water and salt electrolyte disorders, acid-base balance disorders, and accumulation of dialysis metabolites. Nowadays, dialysis treatments significantly reduce the incidence of uremic encephalopathy.

Hyperglycemia and hypoglycemia are commonly seen in elderly patients, and both can result in seizures. Older people using an inappropriate dose of insulin are prone to

hyperglycemia or hypoglycemia, resulting in seizures.<sup>87</sup> Blood glucose is the main energy source of brain cells, abnormal glucose leads to a lack of energy supply with reduced oxygen supply to brain cells, resulting in local or diffuse cerebral ischemia. Patients with non-ketotic hyperosmolar coma have greater possibility of developing seizures than those with diabetic ketoacidosis, which may be due to the anticonvulsant effect of ketosis.<sup>93</sup>

Finally, lifestyle-associated factors, such as alcohol and alcohol withdrawal, also make the elderly more susceptible to a higher risk of acute seizures; although alcohol-associated seizures play a lesser role and such seizures could be self-limiting, they should not be neglected because these seizures often manifest as generalized seizures.<sup>84</sup> A general theory is that alcohol may increase the number of calcium channels and promote seizure activity by augmenting the levels of neurotransmitters.<sup>94</sup>

## Status epilepticus

SE is a neurological emergency, which is defined as the occurrence of two or more convulsive seizures without full recovery of consciousness between the seizures or continuous convulsive activity lasting for more than 10 minutes.<sup>95</sup> In clinical work, SE is not uncommon in the elderly. In one retrospective study, SE occurred in 7.5% patients aged 60 years and older.<sup>69</sup> Drug use is a factor for SE, being mentioned frequently. It is estimated that 15% of patients with seizures secondary to drug use can develop SE, especially with the use of antibiotics.<sup>96</sup>

Penicillins, cephalosporins, carbapenems, and quinolones have been reported to result in SE, particularly when used intravenously at high doses in patients with hepatic or renal dysfunction.<sup>96</sup> Beta-lactam antibiotics and quinolones block gamma-aminobutyric acid and benzodiazepine receptors, and carbapenems and quinolones activate N-methyl-D-aspartate-induced epileptogenesis.<sup>96</sup> In the cephalosporin group, SE has been reported with the use of ceftriaxone, ceftazidime, cefotaxime, and cefepime. Among the carbapenems, imipenem is more seizurogenic than meropenem. Among quinolones, SE has also been reported with the use of ciprofloxacin, ofloxacin, and gatifloxacin.<sup>96</sup>

In addition, extremes of age, low serum albumin resulting in high free drug level, and coadministration of potentially epileptogenic drugs may also contribute to SE.

It is important to choose an antibiotic with low epileptogenic potential and to use an appropriate dose to prevent seizure, especially in patients with renal impairment. There are no reports on SE associated with the use of

aminoglycosides, azithromycin, vancomycin, clindamycin, and teicoplanin, so, these antibiotics may be the best choice for patients with central nervous lesion and renal and liver dysfunction who are prone to seizure.<sup>96</sup>

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## Supplementary material

**Table SI** The summary of the percentage of each cause of new-onset epilepsy in the elderly

Cerebrovascular diseases account for 30%–50%.

Primary neurodegenerative disorders account for ~10%–20%.

Head trauma accounts for 10%–20%.

Brain tumors account for nearly 10%–30%.

One-third to one-half of geriatric epilepsies still have undetected causes, to date.

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