PSYCHIATRIA ET NEUROLOGIA JAPONICA

Review Article

Diagnosis and Treatment of Epilepsy in the Elderly in Psychiatry

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Abstract

Foreign epidemiologic studies have confirmed that the incidence of epilepsy among the elderly is higher than that in children. A study carried out in Hisayama in Japan also revealed that the prevalence of epilepsy was significantly higher in the elderly population (aged≥65 years; 10.3 per 1000) than that in the middle-aged population. As a result, opportunities to treat epilepsy among the elderly are increasing in general psychiatric settings. Among elderly patients, focal epilepsy occurs most commonly and focal (onset) impaired awareness seizures are often observed. However, generalized tonic-clonic seizures are relatively rare. Impaired awareness seizures are not commonly recognized as a symptom of epilepsy; therefore, in order to improve the diagnosis, it is important to encourage the patients and their families to provide detailed descriptions of the symptoms. Video recording a seizure may also prove useful for an accurate diagnosis. The use of anti-depressants may cause nonconvulsive status epilepticus (NCSE). The examination of an electroencephalogram is important for the diagnosis of NCSE because it reveals alternations in the state of consciousness. It is essential to differentiate between geriatric epilepsy and dementia, as transient epileptic amnesia and focal (onset) impaired awareness seizures may be misdiagnosed as dementia. Recent studies reported that epilepsy in the elderly is often comorbid with cognitive decline. Moreover,

epileptiform activity may also suggest cognitive dysfunction. As a consequence, epilepsy in the elderly is important for a differential diagnosis and as a comorbidity of dementia. Furthermore, epileptic discharge may deteriorate cognitive symptoms. Considering that the treatment response is good in the elderly, appropriate therapy may also prevent cognitive dysfunction. Enzyme-inducing anti-epileptic drugs may influence pharmacokinetic interactions, leading to numerous comorbidities, including osteoporosis and lipid metabolism disorder. Therefore, it is important to consider utilizing alternate forms of medication. The diagnosis of epilepsy may also have a social impact, as the safety of patients with impaired awareness seizures is not guaranteed. During treatment, the psychological impacts of this diagnosis must be an important consideration.

Keywords：epilepsy in the elderly, dementia, transient epileptic amnesia (TEA), post-stroke epilepsy, anti-epileptic drugs

Introduction.

In recent years, it has become known that epilepsy is more common in the elderly, and with Japan's aging population, the frequency of epilepsy in the elderly is increasing in psychiatry. It has been reported that seizure control in elderly patients with epilepsy can be improved with appropriate diagnosis and treatment, but the diagnosis can be difficult, including differentiation from dementia. Since epileptic seizures can be the cause of traffic accidents, falls, and injuries, early and appropriate treatment and care are of great clinical and social significance. In this paper, we review the epidemiology, diagnosis, and treatment of epilepsy in the elderly, including its unique pathogenesis.

Abbreviations in the text and tables are as follows.

CBZ：carbamazepine, CLB：clobazam, CZP：clonazepam, DZP：diazepam, ESM：ethosuximide, GBP：gabapentine, LCM：lacosamide, LEV：levetiracetam, LTG：lamotorigine, PB：phenobarbital, PER：perampanel, PHT：phenytoin, PRM：primidone, TPM：topiramate, VPA：valproic acid, ZNS：zonisamide.

I. ILAE Epilepsy Classification 2017

The International League Against Epilepsy (ILAE) released a new epilepsy classification in 2017. Because of some important changes in epilepsy care, a brief overview will be given before the main discussion of epilepsy in the elderly.

One of the major changes is that epilepsy is now diagnosed at three levels: "seizure type," "epilepsy type," and "epilepsy syndrome," so that epilepsy can be classified in different treatment settings. In addition, six "etiologic" diagnoses have been incorporated, as the causative genes have been elucidated and autoimmune mechanisms are known to be involved in the development of epilepsy. In the new epilepsy classification, all three levels of diagnosis should be pursued as much as possible, while simultaneously searching for the etiology of individual epilepsies29) (Figure 1).

In terms of seizure type classification, the term "partial (seizure)" in the old terminology was changed to "focal (seizure)," "simple partial seizure" was changed to "focal aware seizure," and "complex partial seizure" was changed to "focal impaired awareness seizure" 10) (Fig. 2). The term "benign" has been replaced by the terms "self-limited" and "pharmaco-responsive" in consideration of the long-lasting effects on cognitive function and psychosocial effects. The term "comorbidity" was also emphasized because epilepsy can be comorbid with intellectual disability, autism spectrum disorder, depression, etc., and appropriate diagnosis and treatment are important29).

The terminology used in this paper is based on the new epilepsy classification.

II. Characteristics of Epilepsy in the Elderly

1.Epidemiology of Epilepsy in the Elderly

The annual incidence of epilepsy in Minnesota, USA, was 100,000 to 100,000 in people in their 70s and 100,000 to 173 in people in their 80s, compared with an average of 100,000 to 44 in all age groups, indicating a higher incidence of epilepsy in the elderly13) . This report has led to a growing interest in epilepsy in the elderly, even though it was previously thought to be more likely to occur in childhood. The same trend was confirmed in overseas epidemiological studies in other regions such as Sweden and Iceland8)11)25) (Figure 3). A study in Finland showed that epilepsy in the elderly increased over time due to the aging of the population31).

The prevalence of epilepsy in people aged 65 years and older was 10.3/1,000, which was about three times higher than that in people aged 40-64 years (3.6/1,000), confirming the high

prevalence of epilepsy in the elderly in Japan. Fifty-seven percent of epilepsy patients experienced their first seizure at age 65 or older, suggesting a high prevalence of old-onset epilepsy in Japan. In 2017, there were 35.15 million people aged 65 years or older in Japan, and based on the prevalence of epilepsy in the Hisayama study, it is estimated that there are more than 300,000 people aged 65 years or older with epilepsy in Japan.

2.Diagnosis of Epilepsy in the Elderly

According to the conceptual definition of epilepsy, the diagnosis of epilepsy is made when "two unprovoked seizures occurring more than 24 hours apart" are observed. However, in 2014, the ILAE published a practical definition of epilepsy that can be applied to situations that do not meet the criteria for two unprovoked seizures. 9)

Ramsay, R. E. et al.26) reported that the recurrence rate after a first seizure in the elderly is as high as 66-90%, and in view of the practical definition, the elderly are considered to be at high risk of recurrence after a first seizure, and initiation of treatment should be considered even for a single unprovoked seizure.23) In particular, it is advisable to initiate treatment when a causative intracranial lesion or epileptic discharge is identified.

Although electroencephalography (EEG) is important in the diagnosis of epilepsy, the capture rate of epileptic discharges in the interictal period is low in elderly patients with epilepsy. However, the capture rate of epileptic discharges during the interictal period is low in elderly patients with epilepsy. Repeated testing or sleep EEG can increase the capture rate, but often no epileptic discharges are detected. Therefore, it is important to diagnose epileptic discharges not only by EEG but also by seizure symptoms. It is rare to observe seizure symptoms directly in the actual examination room, and there is a limit to the number of interviews that can be conducted. In the case of suspected epilepsy, asking family members to record video of seizures can provide valuable information for diagnosis39).

3.Clinical features of epilepsy in the elderly

The most common seizure type is focal impaired awareness seizures (43%)27). Therefore, seizure symptoms caused by temporal lobe epilepsy should be considered first in daily practice. In the elderly, seizures may be characterized by immobility or cessation of movement, and autonomic symptoms are relatively rare. After a seizure, the patient tends to become dizzy, and the seizure tends to be prolonged. Because seizure symptoms

and dazed state are often misunderstood by family members as symptoms of dementia, it is important to elaborate on the questionnaire by specifically asking whether the patient stares at a single point, does not respond to calls, gags his mouth, repeats the same action, or walks around aimlessly afterward. Table 1 shows the clinical picture of epilepsy in elderly patients.3) If in doubt, actively collect information for diagnosis.

4.Epilepsy in the Elderly

The elderly are more likely to present with status epilepticus, and both convulsive status epilepticus (CSE) and non-convulsive status epilepticus (NCSE) are common39) . NCSE is defined as persistent seizures without convulsions due to overexcitability of the brain, and is a condition rather than a disease name.39) NCSE may occur against a background of severe organic brain disease, such as acute encephalopathy, or may include mild impairment of consciousness due to antipsychotic drugs or electrolyte abnormalities. In the latter type of NCSE, chronic repetitive disorientation and decreased responsiveness occur. Taniguchi, G. et al.35) reported three cases of NCSE in the elderly due to the use of therapeutic doses of antidepressants, suggesting the importance of differentiating NCSE from worsening psychiatric symptoms such as depressive stupor, which may be encountered in psychiatric practice. NCSE can be difficult to diagnose without electroencephalography (EEG), and EEG should be considered in elderly patients with fluctuating cognitive decline.

5. Etiology of Epilepsy in the Elderly

The most common etiology of epilepsy in the elderly is cerebrovascular disease, trauma, brain tumor, and dementia.26) Cerebrovascular disease accounts for 30-50% of epilepsy cases, and in a Japanese epidemiological study,34) cerebrovascular disease accounted for 48% of epilepsy cases. The second most common cause was degenerative diseases such as Alzheimer's disease, which accounted for 20% of the confirmed etiology26). On the other hand, there are many cases in which no apparent etiology can be found33) , and these have been the focus of particular research in recent years.

Epilepsy, which is related to autoimmune mechanisms, has been attracting attention as one of these diseases, and is often diagnosed and treated as another disease because of its subacute to chronic course and the fact that symptoms may include only epileptic seizures or psychiatric symptoms. Autoimmune encephalitis presents as limbic encephalitis and is

often accompanied by focal impaired awareness seizures, impaired memory, behavioral abnormalities, and psychiatric symptoms28) . It is known that LGI1 and CASPR2, which are proteins constituting VGKC, are closely associated with limbic encephalitis.36) Frequent and homogeneous dystonic seizures of the unilateral face and upper limbs lasting less than 3 seconds are called faciobrachial dystonic seizure （FBDS） . It has been shown to be specific to the anti-LGI1 antibody encephalitis described above.

Second, amygdala enlargement has also attracted attention as an etiology of epilepsy. Medial temporal lobe epilepsy with amygdala enlargement often develops after middle age, is relatively responsive to drugs, and improves with treatment. However, there are still some points that remain to be fully elucidated. It has been suggested that amygdala enlargement is related to the autoimmune mechanism described above18).

III. Characteristic Seizures and Differential Diseases in Epilepsy in the Elderly

1. Transient epileptic amnesia

In 1998, Zeman, A. et al.40) proposed the diagnostic criteria shown in Table 2 for TEA as "frequently witnessed amnesic seizures with normal cognitive function and seizures thought to be caused by epilepsy.

According to a report of 50 cases by Butler, C. R. et al.5), the average age of onset of TEA was 62 years, the average frequency was once a month, and the average duration was 30 to 60 minutes. Convulsive seizures are less common. TEA also responds well to antiepileptic drugs (96%), making it a treatable condition.

In addition to amnesic attacks, TEA is said to be associated with three other characteristic memory disorders6): 1) accelerated long-term forgetting, in which new memories are rapidly lost within a few weeks; 2) autobiographical amnesia, in which significant personal memories experienced in the distant past are lost; and 3) topographical amnesia: loss of recognition of familiar places. When the above features of memory impairment are observed, an epileptic condition should be differentiated. The pathogenesis of amnesic seizures and these characteristic memory deficits is unknown, but they are thought to be due to excessive neuronal discharge, as they improve markedly with antiepileptic drug treatment.

2.Differentiation of epilepsy in the elderly

1) Loss of concentration

The incidence of syncope increases

significantly in patients older than 70 years. When an elderly patient presents to the hospital with a complaint of transient loss of consciousness seizure, it is important to differentiate syncope from epilepsy, considering its lethality22). Although it is difficult to differentiate between syncope and epilepsy because of the similarity of the seizure situation, a detailed history should be taken, paying attention to the points of differentiation as shown in Table 3. However, pallor is characteristic of syncope, and the presence of autonomic symptoms increases the possibility of epilepsy. In terms of aura, blackness before the eyes is observed in syncope, while patients with temporal lobe epilepsy may be aware of focal aware seizures, such as déjà vu and abdominal ascending sensation.)

2)Acute symptomatic presentation

Acute symptomatic seizures are convulsive seizures that are often seen in the emergency department. When seizures are seen in acute illnesses such as acute stroke, encephalitis, metabolic disorders, electrolyte abnormalities, infections, and drug addiction/withdrawal, they are distinguished from epilepsy as a chronic disease. When the condition of the primary disease subsides, the seizures may also subside, so the identification and treatment of the primary disease should be prioritized15).

3) REM sleep behavior disorder

It is important to distinguish REM sleep behavioral disturbances from focal impaired awareness seizures, which often occur in older age. However, in the case of focal impaired awareness seizures, the patient is unresponsive and does not remember the event after the seizure ends. However, in the case of REM sleep behavioral abnormalities, reactivity is maintained, and the patient can be awakened and can later reflect on his or her actions.

IV. Relationship to dementia

1. Comorbidity with dementia

The risk of seizures during the course of Alzheimer's disease (AD) is 6 to 10 times higher than in the general population.14) Beagle, A. J., et al.2) reported that the seizure rate in AD and dementia with Lewy bodies (DLB) was 13.4% and 14.7%, respectively, and the seizure rate in DLB increased with the progression of dementia. In frontotemporal dementia (FTD), the seizure rate was 3.0%, and the incidence of epilepsy was lower than in AD and DLB.

In a study of 35 patients with AD and epilepsy by Vossel, K. A. et al.37), 77% developed epilepsy at the same time or earlier than the onset of AD. On the other hand, 91% of the patients developed epilepsy at or after the onset

of some cognitive decline. The Mini-Mental State Examination (MMSE) score at the onset of epilepsy was above the cutoff of 24 points in 57% of the patients (Fig. 4). It was previously thought that epilepsy appeared only in the late stages of dementia, but this is not the case. The study revealed that epilepsy often develops between the onset of cognitive decline and the onset of AD.

A case report by Lam, A. D. et al.16) is interesting as evidence to suggest increased epileptic activity in AD: simultaneous recording of scalp EEG and intracranial foramen ovale electrodes in AD patients revealed epileptic discharges in the hippocampal region on foramen ovale electrodes that were not seen on scalp EEG. Vossel and Lam's report suggests that hippocampal overactivity occurs during the period from mild cognitive impairment to the onset of AD, resulting in increased epilepsy.

2.Effects of epilepsy on cognitive function

Vossel et al.38) also investigated the effects of epileptic discharges on cognitive function in AD patients. Comparing the AD group with epileptic discharges captured by long-term video EEG and magnetoencephalography with the AD group without epileptic discharges, the group with epileptic discharges showed a significant decline in MMSE scores over time (3.9 points/year vs. 1.6 points/year, P=0.006). This suggests that epileptic discharges accelerate the progression of cognitive decline in AD patients.

Shiozaki, K. et al.30) then reported changes in cognitive function after treatment of epileptic discharges. 50 cognitively impaired patients with epileptic discharges on EEG were included, and changes in MMSE were recorded before and after treatment with antiepileptic drugs. The results showed that antiepileptic drug treatment increased the MMSE scores of 60% of the patients, with a significant increase in the score of Serial 7, which reflects attention-based computational ability, suggesting that the treatment of epileptic discharges resulted in the recovery of attention. Epileptic discharges may be an aggravating factor that interferes with normal brain function and leads to more progressive cognitive impairment, and appropriate treatment may be protective of cognitive function.

These findings suggest that epilepsy is not only a differential disease from dementia, but also a comorbidity and an aggravating factor.

V. Treatment of Epilepsy in the Elderly

1.Antiepileptic drug therapy for the elderly

In the elderly, drug metabolism is slowed by aging, and epileptogenicity is generally thought to decrease with age. Therefore, the dose should be started much lower than the standard adult dose (1/4 to 1/2), titrated upward over a sufficient period of time, and maintained at a lower dose.

2. Prognosis of epilepsy in the elderly

In a study of seizure control rates by age of onset of epilepsy,19) 65% of patients with epilepsy younger than 20 years of age, 53% of patients with epilepsy between 20 and 64 years of age, and 85% of patients with epilepsy older than 65 years of age responded well to treatment. In a longitudinal study by Tanaka, A. et al.33) in Japan of 54 elderly patients with epilepsy who developed epilepsy at age 65 or older, 96% maintained seizure resolution for 1 year after treatment with antiepileptic drugs.

3. Enzyme-inducing effects of antiepileptic drugs

In the treatment of elderly patients with epilepsy, it is essential to consider the interaction of antiepileptic drugs with other drugs for the treatment of physical complications. The enzyme-inducing antiepileptic drugs PHT, CBZ, PB, and PRM are known to induce cytochrome P450 (CYP) and glucuronide conjugation in the liver. These drugs not only affect other concomitant antiepileptic drugs, but also interact with non-antiepileptic drugs (Xa inhibitors, antiplatelet agents, warfarin, statins, acetaminophen, prednisolone, calcium channel blockers, etc.), accelerating the metabolism of the concomitant drugs and reducing their efficacy. In patients with epilepsy complicated by psychiatric symptoms, antidepressants and antipsychotics may be used concomitantly, but care must be taken because enzyme-inducing antiepileptic drugs also reduce the effects of these drugs. The effect of enzyme-inducing antiepileptic drugs on the blood concentration of psychotropic drugs is shown in Table 4.)

Induction of CYPs by enzyme-inducing antiepileptic drugs increases the catabolism of active vitamin D [1,25-(OH)2-D3] in the liver, resulting in drug-induced osteoporosis. Similarly, CYPs increase cholesterol production, which is a risk factor for abnormal lipid metabolism and increases the risk of ischemic heart disease and cerebrovascular disease4). Therefore, enzyme-inducing antiepileptic drugs are not recommended for use in the elderly.

LTG, TPM, and CZP are said to have both enzyme-inducing and inhibitory effects, while LEV, ZNS, GBP, CLB, ESM, LCM, and PER are non-enzyme-inducing antiepileptic drugs without

enzyme-inducing effects. The benefit of non-enzyme-inducing antiepileptic drugs in the treatment of epilepsy in the elderly has been significant, as the elderly are more likely to have or develop complications later in life. The Epilepsy Clinical Practice Guidelines 201823) recommend LEV, LTG, and GBP for focal epilepsy in elderly patients with comorbidities and comorbidities, and exclude CBZ as an enzyme inducer. A recent meta-analysis17) of pharmacotherapy for epilepsy in the elderly reported that LTG was better tolerated than CBZ, although there was no difference in efficacy between LTG and CBZ, and that LEV may provide better seizure control than LTG. However, the possibility of severe drug eruption caused by LTG should be carefully considered.

4. Side effects of antiepileptic drugs

Common side effects of antiepileptic drugs include drowsiness, lightheadedness, and impaired concentration, and a recent systematic review12) reported an association between antiepileptic drug use and falls in the elderly. Since falls can significantly impair ADL, caution is required, and benzodiazepines (CLB, CZP, DZP) should be avoided in the elderly.

In light of the impact of antiepileptic drugs on cognitive function, it was reported that regular use of antiepileptic drugs significantly increased the risk of developing dementia (adjusted odds ratio=1.28, 95% confidence interval=1.14-1.44), and the risk was particularly high for anti The risk is especially high for antiepileptic drugs (PB, PRM, PHT, ESM, CZP, CBZ, VPA, TPM, ZNS), which are known to have adverse effects on cognitive function.32) The use of antiepileptic drugs that are known to have no adverse effects on cognitive function (LTG, GBP, LEV, LCM) should be considered when selecting antiepileptic drugs for the elderly.

Conclusion.

In the field of psychiatry, psychiatric disorders (anxiety disorders, depression, psychotic episodes) in the elderly should be differentiated from epilepsy and its comorbidity. It is not uncommon for a patient who has been treated as a psychiatric patient and has been intractable for a long time to have epilepsy as a symptom24). It should also be noted that many antipsychotic drugs lower the convulsive threshold.

In recent years, there have been many reports of automobile accidents involving the elderly, and although not all of these accidents occur, it is possible that epileptic seizures are part of the cause. It has been reported that the risk

of motor vehicle accidents is increased in patients with epilepsy.7) Therefore, proper diagnosis is of great social significance.

Finally, it is important to remember that the psychosocial aspects of epilepsy should be taken into account when making a diagnosis, especially in the elderly, who may have different perceptions of epilepsy and the psychological burden of being diagnosed.

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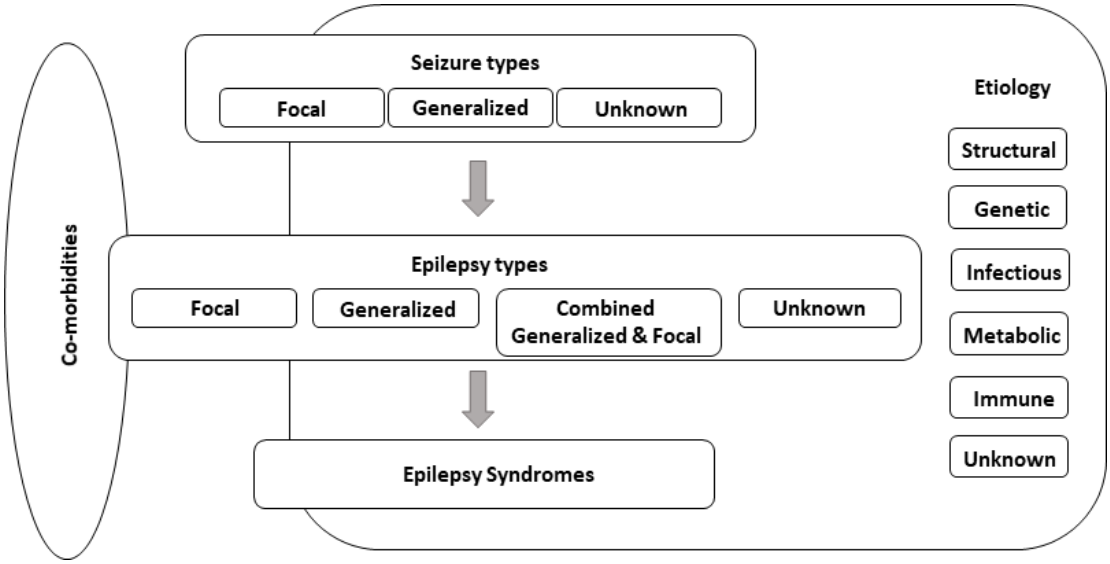


Figure 1 ILAE Epilepsy Classification 2017: Framework for classification of the epilepsies
(Modified from reference 29)

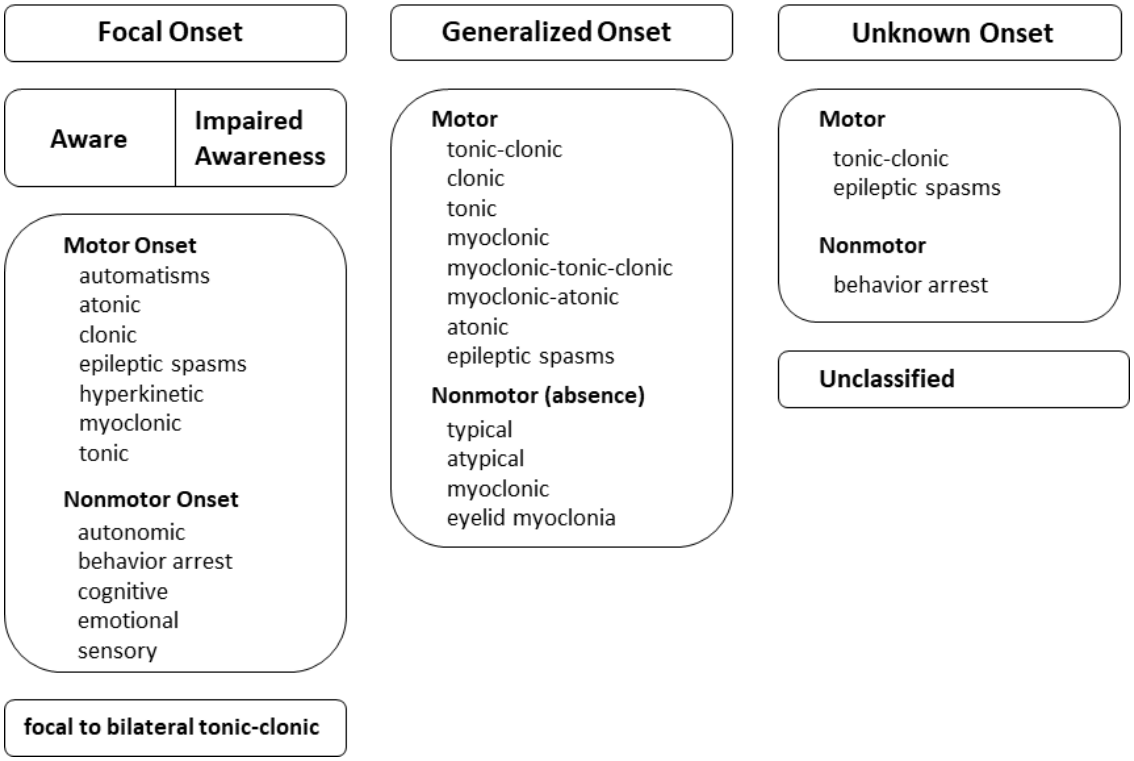


Figure 2 ILAE 2017 Classification of Seizure Type
(Modified from Reference 10)

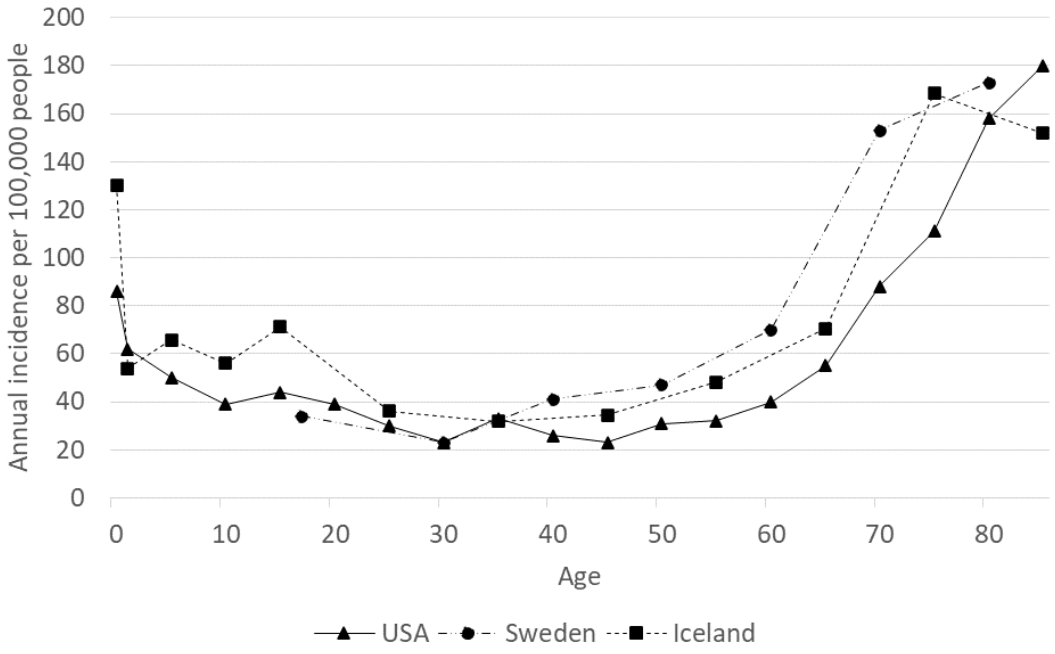


Figure 3 Epilepsy incidence by age
It can be seen that the incidence of epilepsy increases after the age of 60.
(Compiled from references 11, 13, and 25)

• Confusion, behavioural change, or unresponsiveness not associated with loss of postural control
• Loss or impairment of consciousness
• Twitching, involuntary movement, or sensory disturbance of a limb, limbs, or face without loss of consciousness
• Recurrent episodes of troublesome sleep disturbance
• Frequent falls about which the patient has no recollection

Table 1: Clinical clues to the diagnosis of epilepsy in elderly people
(Cited from reference 3)

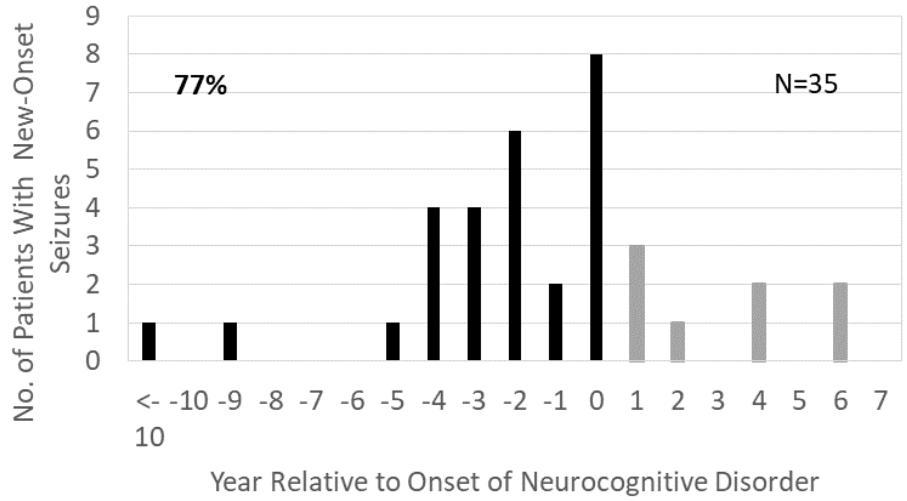
• A history of recurrent witnessed episodes of transient amnesia
• Cognitive functions other than memory judged to be intact during typical episodes by a reliable witness
• Evidence for a diagnosis of epilepsy based on one or more of the following:
a. epileptiform abnormalities on electroencephalography
b. the concurrent onset of other clinical features of epilepsy (e.g. lip-smacking, olfactory hallucinations)
c. a clear-cut response to anticonvulsant therapy.

Table 2: Diagnostic criteria for transient epileptic amnesia
(Cited from reference 6)

		Syncope	Epileptic seizure
Symptoms before seizure	Triggers (emotion, position, etc.)	relevant	irrelevant
	Sweating	with sweating	without sweating
	Aura	dimmed vision	deja vu, epigastric distress
	Pallor of the face	pallor	not pallor

Seizure symptoms	Cyanosis	rare	sometimes
	Duration of unconsciousness	within 30 seconds	more than one minutes
	Convulsions	a few seconds to 15 seconds	1 to 2 minutes
	Automatism	rare	often (in focal onset impaired awareness seizure)
	Tongue biting	rare	occasionally (lateral aspects of tongue)
	Hypersalivation	rare	often
Symptoms after seizure	Dazed and disorientation	rare	often
	Myalgia and headache	rare	often
	Elevation of lactic acid and CK	rare	often (in convulsion seizure)

Table 3: Differentiation between syncope and epileptic seizures
CK: Creatine kinase
(Modified from Reference 1)



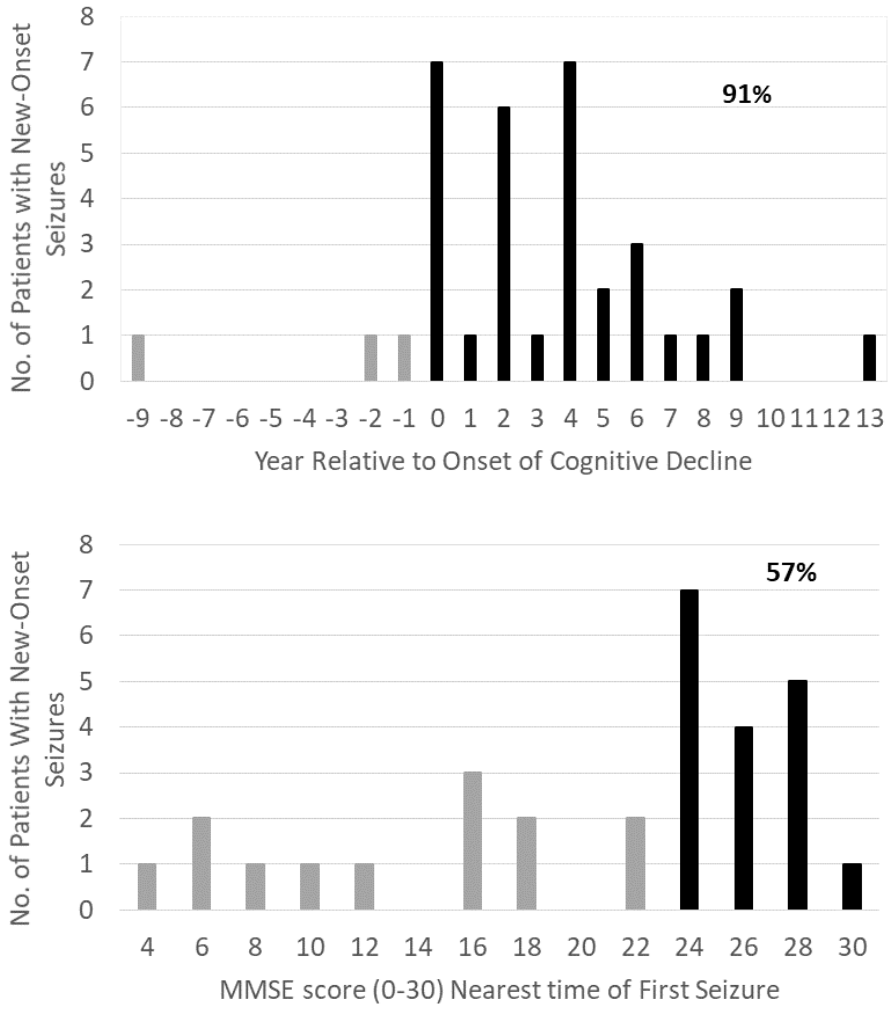


Fig. 4 Onset of epilepsy associated with Alzheimer's disease
AD: Alzheimer's disease, MMSE: Mini-Mental State Examination
(Modified from Reference 37)

AED	Effect on target enzymes	Target enzymes	Effect on concentration of antipsychotics or antidepressant	
			Elevate	Decrease
PHT	Induce	CYP2C9, CYP2C19, CYP3A, UGT		quetiapine, clozapin, paroxetine (about 25%), sertraline (about 25%), mirtazapine, mianserin, TCA
CBZ	Induce	CYP1A2, CYP2C9, CYP2C19, CYP3A, UGT		haloperidol (20-80%), aripiprazole(71-88%), clozapine(50%), olanzapin(36-71%), quetiapine(over 85%), risperidone, mirtazapine, mianserin, TCA

PB/ PRM	Induce	CYP1A, CYP2A6, CYP2B, CYP2C9, CYP2C19, CYP3A, UGT		chlorpromazine, clozapin, mirtazapin, mianserin, paroxetine (about 25%), sertraline(about 25%),TCA
CZP	Induce	CYP3A4, UGT		
VPA	Inhibit	CYP2C9, UGT, epoxide hydrolase	amitriptyline, nortriptyline, clomipramine, paroxetine	aripiprazole (25%)
LTG	Induce	UGT		
	Inhibit	UGT, CYP2C19		
TPM	Induce	CYP3A4		haloperidol(about 30%),
	Inhibit	CYP2C19		lithium(when TPM600mg/day used together)

Table 4 Effects of enzyme-inducing antiepileptic drugs on blood concentrations of psychotropic drugs

CYP: cytochrome 450, UGT: UDP-glucuronosyltransferase, TCA: tricyclic antidepressants, AED: antiepileptic drugs
(Adapted from reference 20)