

Review Article

Epilepsy in the Elderly

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Abstract

Both incidence and prevalence of epilepsy are high among the elderly patients. Epilepsy in the elderly differs in etiology, clinic features and prognosis. The most common etiological factor of epilepsy in the elderly is cerebrovascular diseases. Although most of the seizures in elderly patients are of focal onset, with or without secondary generalization, the presentation of seizures may be nonspecific. The diagnosis of epilepsy in the elderly patients may be difficult because of subtle semiological findings, co-morbid diseases, medications and age-related cognitive difficulties. A detailed history, a comprehensive neurological examination, routine laboratory tests, EEG and neuroimaging modalities are the cornerstones of diagnostic evaluation. Treatment of epilepsy in the elderly requires an understanding of the etiologies, medical and psychological aspects of this age group and should be based on careful assessment of risk/benefit profiles of antiepileptic drugs. The choice of antiepileptic drugs is also determined by side-effects, tolerability, drug interactions and pharmacokinetic profiles.

INTRODUCTION

The incidence of new onset seizures and epilepsy in the elderly is higher than any other age group [1]. In most studies, the elderly are generally considered as the people over the age of 65, but in some studies people over the age of 60 years are considered as the elderly population. The elderly is the part of the population that is most rapidly increasing as a result of increasing life expectancy and the aging of the baby-boomer generation [2]. The modification of cardiovascular risk factors, health screenings and preventive therapies resulted in longer life expectancies. Age-related neurological disorders such as cerebrovascular and neurodegenerative disorders are the most common etiological factors for epilepsy in the elderly.

Both provoked and unprovoked etiologies should be considered for an individual presenting with a seizure [3]. Metabolic conditions, cardiac insufficiency, vasovagal syncope, prescription and nonprescription medications, herbal and other supplements, alcohol and recreational drug use are some of the provoked etiologies. Epilepsy is defined as the occurrence of at least two unprovoked seizures separated 24 hours apart, but the latest international consensus definition only requires a single epileptic seizure in association with an enduring disturbance of the brain capable of giving rise to other seizures [4]. Many of the etiologic factors leading to a first epileptic seizure in the elderly cause a predisposition to seizures [2].

Diagnosing epilepsy in the elderly is challenging as reliable history is often difficult to obtain and Electroencephalography (EEG) findings may be nonspecific. Treatment should be based on careful assessment of the patient's age, hepatic and renal functions, co-morbid conditions and side effects of the

medications. Risk/benefit profiles of various Antiepileptic Drugs (AEDs) should be compared carefully in this specific population [5].

Approach to elderly population requires knowledge and experience in order to increase the quality of life and to decrease the cost of health care. Old people with epilepsy have different problems than the young people with epilepsy. For this reason, further studies are still needed to identify the special issues related to the elderly population.

Incidence and prevalence

The incidence of acute unprovoked seizures, acute symptomatic seizures and Status Epilepticus (SE) increases with advancing age [6]. The incidence of seizures is highest in patients over 60 years. The incidence of new onset epilepsy has been documented as 90 per 100,000 between 65 and 69 years of age and increases to 150 per 100,000 in people older than 80 years [7]. The prevalence of epilepsy is 1.5% for people over the age of 60, twice as high as the prevalence among younger adults and by the age of 80 three times that reported in children [5]. In nursing home residents, the prevalence of epilepsy exceeds 5%. Studies on elderly nursing home residents found that almost 10% were taking an AED for the indication of seizures or epilepsy [8,9].

Thirty per cent of acute seizures in elderly people presents as SE which carries a mortality approaching 40% [10,11]. The incidence of SE has been estimated based on various population-based studies conducted in various countries. These studies have reported the incidence of SE in the elderly from 15.5-86/100,000 as compared to 4.2-5.2/100,000 in young adults [12-14]. SE can occur as convulsive or non-convulsive SE. Increasing age and the underlying medical conditions have been found as the main

predictors of mortality associated with generalized convulsive SE [13].

Etiology

Epilepsy is usually diagnosed as the occurrence of two or more unprovoked seizures. Older people presenting with an unprovoked seizure are more likely to develop seizure recurrence than younger adults [10]. Even with the advance of diagnostic investigations, between 25 and 45% of new epilepsy cases among individuals older than 60 years, have no obvious etiology [6].

The most common cause of provoked seizures in the elderly is acute cerebrovascular diseases [2,5,6,9,10,15]. The other etiological factors contributing to seizures and epilepsy in elderly are neurodegenerative diseases, brain tumors, Central Nervous System (CNS) infections, toxic/metabolic syndromes and head trauma. Also drugs including antipsychotics, antidepressants, antibiotics, theophylline, levodopa and thiazide diuretics may precipitate seizures.

The Veterans Administration Cooperative Study (VACS) #428 revealed that cerebrovascular etiologies included cerebral infarction in 30%, cerebrovascular arteriosclerosis in 16% and cerebral hemorrhage in 2% of patients [16]. Remote traumatic brain injury was found in 7% and other brain lesions such as AVM and brain tumors were detected in 2% of the patients included in the VACS #428 study. Almost 24% of the patients had an unknown etiology for the seizures. In the remaining 18% of the patients, other known causes were responsible for the seizures [16]. The rate of occurrence of 'vascular epilepsy after stroke ranges from 4% to 15%. Poststroke epilepsy usually occurs within 3 months to 1 year after the vascular event [15]. Seizures are described as early (<7 days) and late (>7 days) after a stroke. Predictors for poststroke seizures have been reported as hemorrhagic stroke, poor neurological status, partial anterior circulation syndrome and cortical localization in various studies. Predictors for poststroke epilepsy include hemorrhagic stroke, venous infarction, right hemispheric stroke especially in the middle cerebral artery territory and occurrence of a late onset seizure [5]. Age at onset of stroke and cardioembolic versus atherothrombotic stroke type were found not to be associated with poststroke epilepsy [5,17,18].

Neurodegenerative disorders such as dementias, have been considered as significant causes of seizures. Alzheimer Disease has been associated with higher risk for developing seizures than other dementias [2]. A younger age of dementia onset and advanced stage of dementia were the factors associated with seizure occurrence [19].

Seizures may be the first sign of brain tumors in 50% of the patients developing seizures after the age of 60 years [20]. Low-grade astrocytomas, oligodendrogliomas, mixed gliomas, anaplastic astrocytomas and meningiomas have shown to be related with seizures at presentation. Seizures occur in 15% of patients with metastatic brain tumors [21].

Head trauma, CNS infections, alcohol use and acute alcohol withdrawal, electrolyte and metabolic disturbances, various drugs taken by elderly are the other common risk factors for new-onset seizures.

Clinical features

The diagnosis of epilepsy in the elderly patients may be difficult because of subtle semiological findings, co-morbid diseases, medications and age-related cognitive difficulties [2,15]. The presentation of seizure may be nonspecific. Up to 70% of seizures in elderly patients are of focal onset, with or without secondary generalization [22]. Complex Partial Seizures (CPS) are the most common type of seizure. Simple partial seizures occur less frequently and they are mostly associated with motor manifestations [15]. Generalized seizures may be seen in patients with a history of anoxia and neurodegenerative diseases.

The clinical manifestations of CPS in the elderly differ slightly from that of younger patients. Complex partial seizures may present as memory disturbances, confusion, bizarre behaviour or unresponsiveness [5,10]. CPS in the elderly rarely begin with an aura. Auras, when present, may manifest in a nonspecific way such as dizziness [6]. An older individual's seizure focus is more likely to be extratemporal, most often in the frontal lobe. The variation in the clinical presentation of seizures in the elderly may be linked to the anterior frontal cortical areas of the brain that are affected in cerebrovascular diseases [7]. Postictal confusion may last for hours, days or weeks and may even mimic dementia. This prolonged postictal confusion state may contribute to the delayed diagnosis of epilepsy in the elderly [2].

Differential diagnosis

A wide range of conditions may mimic seizures. Cardiovascular diseases should be considered in the differential diagnosis of seizures in the elderly [23]. In the elderly syncope may present with convulsive motor movements and a transient confusional period may be experienced after a syncopal episode. The use of diuretics and antihypertensive medications predisposes the elderly to syncope [24]. Cardiac arrhythmias should always be ruled out in the differential diagnosis of epilepsy in the older individuals.

Transient ischemic attacks (TIAs) may also mimic seizures. TIAs present with negative symptoms as opposed to the positive symptoms of epileptic seizures. Besides, TIAs last for minutes or hours and consciousness is usually preserved. Transient global amnesia, vertigo and migraine are the other neurological conditions that may resemble seizures.

Sleep disorders such as narcolepsy, rapid eye movement sleep disorders and some metabolic disturbances such as porphyria may be confused with seizures and they must be ruled out if epilepsy is suspected [5,6].

Diagnostic evaluation

A detailed history obtained from both the patient and the witnesses and a comprehensive neurologic examination represent the most important parts of the clinical diagnosis of epilepsy in the elderly. Routine laboratory tests, neuroimaging investigations and EEG should be performed. Because of the broad differential diagnosis in this older age group, additional tests should be considered in order to evaluate especially the cardiac and cerebrovascular diseases [15]. Arterial blood gas testing may reveal hypoxia, hypercarbia, respiratory or metabolic acidosis or alkalosis. An Electrocardiogram (ECG) and a chest radiograph

should be done. Since syncope and cardiac arrhythmias are very important in the differential diagnosis in this age group, Holter monitoring and tilt table testing may be added to diagnostic tests [9].

Elderly patients with seizures should be evaluated with one of the neuroimaging modalities. Computed Tomography (CT) should be used in the emergency situation to exclude hemorrhage or large mass lesions [9]. In other situations, magnetic resonance imaging is the imaging procedure of choice and if possible, it should be performed with gadolinium administration for enhancing the detection of tumors and infections.

EEG is essential in the evaluation of seizures. The presence of epileptiform activity is less frequent in the elderly population. In a study, it was reported that only 26-35% of patients over the age of 65 years had interictal epileptiform activity detected on routine EEG [25]. Routine EEG recorded within 24h after the seizure increases the likelihood of detecting epileptiform activities. If necessary, routine EEG investigation should be followed by sleep or sleep-deprived EEGs [26,27]. Prolonged EEG monitoring may be required in establishing a correct diagnosis [28,29]. It is beneficial to monitor ECG during EEG investigation because cardiac diseases may mimic epilepsy. Clinicians should be aware of the non-epileptiform EEG findings that are not associated with epilepsy for the evaluation of the EEGs of the elderly. These non-epileptiform EEG findings include intermittent focal slowing, especially in the temporal region, frontal rhythmic delta activity associated with the onset of drowsiness, small sharp spikes (SSS), Benign Epileptiform Transients of Sleep (BETS), Subclinical Rhythmic Electrographic Discharges of Adults (SREDA) and wicket spikes [9,15].

Treatment

There are special considerations in the elderly that must taken into account in treatment decision. For provoked seizures, provocative factors should be detected and adequately corrected. If an unprovoked seizure is present, AED therapy is indicated according to the likelihood of seizure recurrence [30,31]. A causative brain lesion, an epileptiform EEG or the request of the patient usually enable the clinicians to initiate an AED therapy. Generally an AED therapy is indicated in case of an underlying Central Nervous System (CNS) lesion. In other situations, the decision for treatment depends on an individual basis weighing the advantages versus disadvantages of an antiepileptic therapy [9]. Risks and benefits of seizures should be discussed with the patient and the family. An AED therapy in the elderly possesses greater risks in terms of side effects, adverse drug interactions and toxicity due to diminished renal and hepatic functions [5]. However, initiating an AED therapy also has favorable effects such as maintenance of independence, prevention of injury and avoidance of potential medical complications of a prolonged seizure [9]. In the prospective multicentre study of early epilepsy and single seizures (MESS), it has been shown that compared with deferring treatment until further episodes have occurred, immediate treatment after a first unprovoked seizure does not improve the long term remission rate [32].

Pharmacokinetic changes in the elderly include decreased plasma protein binding, increased volume of distribution

for lipophilic drugs, reduced efficiency of drug metabolizing pathways, decreased drug clearance and prolonged elimination half-life [33,34]. Pharmacodynamic changes include alterations in brain neurotransmitters, homeostatic mechanisms, receptor affinity and decreased number of receptors. Saturation of the decreased number of receptors easily leads to an increase in the concentration of unbound free proportion of AEDs. As a result, the risk of neurotoxicity increases despite total serum drug levels in therapeutic range [35].

Elderly epilepsy patients often have other illnesses requiring additional medications that may contribute to drug interactions. Enzyme inducing antiepileptic drugs can increase hepatic metabolism of anticoagulants, steroids and chemotherapeutic agents causing decreased efficacy. On the other hand, valproic acid which is a hepatic enzyme inhibitor drug can increase levels of phenytoin, carbamazepine and phenobarbital when used as add-on therapy [9].

Phenytoin, phenobarbital, carbamazepine and sodium valproate are effective, traditional antiepileptic medications that are highly protein bound and hepatically metabolized. Monitoring of not only their free but also total drug concentrations is necessitated. It has been shown that they have similar efficacy. Phenytoin and carbamazepine are hepatic enzyme inducers which may cause drug interactions with other drugs. Sodium valproate has been used in both partial and generalized onset seizures and has also been shown to be effective in treating neuropsychiatric disturbances seen in patients with the diagnosis of dementia. However it may cause weight gain and tremor. In the elderly, sodium valproate may also cause parkinsonism which is reversible in six months after the cessation of the therapy. Phenobarbital is very effective, cheap but it may cause significant sedation and cognitive side effects.

Newer antiepileptic medications have fewer drug interactions and side effects. They have renal or nonoxidative hepatic metabolism and low protein binding [9]. Gabapentin is renally excreted and do not have any significant drug interactions. However it may cause considerable sedation. Lamotrigine is effective in both generalized and partial onset seizures. The most serious side effect is rash which is dependent on the rate of titration. Topiramate has a broad spectrum of activity. Weight loss, nephrolithiasis and cognitive changes are the most common side effects. Levetiracetam is effective, well-tolerated and possesses the advantage of not having drug interactions and rapid titration but it may cause behavioral changes in some patients. Dizziness is the most common side effect of levetiracetam. Zonisamide has the advantage of dosing once a day but slow titration is needed.

There exist various studies on antiepileptic drug therapy and on the comparison of them with each other. Willmore reported that newly developed drugs without enzyme induction effects and renal routes of excretion might be more favorable for use in elderly population [36]. Although there are other studies suggesting that new antiepileptic drugs offer potential advantages over the traditional drugs in that they have fewer drug interactions and a more favorable side-effect profile, further clinical trials evaluating their use in the elderly are required [5,7,9].

Since AED therapy in the elderly possesses greater risks in terms of side effects, drug interactions, toxicity due to diminished renal and hepatic function, prescribing AEDs in situations where they are not indicated, fast titration of medication, prescription of high dosages, excessive polypharmacy and unnecessary prolongation of AED therapy should be avoided [5].

CONCLUSION

Clinicians should understand the etiological factors and subtle clinical features of the elderly patients and should consider seizures within the differential diagnosis of neurological symptoms in this age group. The choice of AED therapy requires consideration of factors specific to the elderly in terms of lower doses, slower titrations, pharmacokinetic changes, treatment responses, drug interactions and co-morbidities. Further studies are still necessary to determine the best treatment options in this age group regarding both the traditional and the new-generation AEDs.

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