Epilepsy in Aging Veterans

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Introduction

The elderly are the fastest growing segment of the population in developed countries, and in the next few decades, 20% of the population will be over the age of 65 years.[1,2] This segment of the population has the highest incidence of new-onset epilepsy and poses unique challenges to management.[2,3] Many older patients have comorbid conditions that can affect epilepsy, and the medications they take for these conditions can interact with antiepileptic drugs (AEDs). Moreover, most AEDs are not approved based on studies in older patients, which introduces uncertainty about efficacy and safety of these drugs in the elderly.[2] Cellular changes also occur in the aged epileptic brain; there is decreased neurogenesis of dentate granule cells but a concomitant increase in hippocampal neurogenesis.[2] Older veterans have all the same concerns as other older patients; however, they have several other challenges that make epilepsy management more complicated. This paper will identify the issues faced by older veterans with epilepsy and offer suggestions on management.

As noted above, recent epidemiologic data have shown that the incidence of unprovoked seizures in the elderly approaches 200 per 100,000, a figure almost 4 times as high as young and middle-aged individuals.[4] Research from the Department of Veterans Affairs (VA) indicates that the incidence of epilepsy in older veterans may be about 6 to 10 times higher than in younger individuals.[5]

Etiology

The etiology of seizures in older veterans may be more easily determined than in younger patients. Data about etiology in older veterans come from the VA Cooperative Study (VACS) #428.[6] In this study, primary etiology was cerebral infarction (29.9%), arteriosclerosis (15.7%), head trauma (7.1%), unknown

causes (24.0%). It is well known that traumatic brain injury (TBI) can cause epilepsy. Data from the Vietnam Head Injury Study (VHIS) established that more than 50% of patients with TBI developed epilepsy within 15 years.[7] Most of these patients had penetrating injuries and most developed epilepsy in the first 12 months. However, the most recent data from this study show that some patients developed epilepsy more than 14 years after head injury. This means that veterans of Vietnam and Korean wars may still continue to be diagnosed with epilepsy, and that veterans of more recent conflicts who suffered TBI will continue to be diagnosed with epilepsy for many years to come.

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Risk factors

Risk factors for new-onset epilepsy in older veterans have also been evaluated. Individuals with cerebrovascular disease and dementia have an odds ratio (OR) of 4.14 for developing epilepsy, and those with only cerebrovascular disease have an OR of 3.50.[3] Patients with brain tumor, head injury, and other central nervous system (CNS) disease have an OR of 2.14, 2.11, and 1.57, respectively. Among aged veterans, African Americans were more likely than Caucasians to develop epilepsy.[3] These risk factors should prompt providers to be especially mindful of seizures in older veterans with odd spells and episodes of fluctuating mental status.

Diseases that increase the likelihood of older veterans for developing epilepsy are also some of the most common comorbid conditions associated with epilepsy. Stroke and cardiac disease are very common (seen in about 25%-50% of veterans with epilepsy). Cognitive impairment is also frequently associated with epilepsy and may be further complicated by comorbid Alzheimer’s disease, Parkinson’s disease, multiple cerebral infarctions, alcohol-related conditions, and normal pressure hydrocephalus.[5]

Diagnosis of epilepsy in elderly veterans

As common as epilepsy is in elderly veterans, diagnosis is often delayed or missed all together. Only a minority (27%) of these patients are evaluated and diagnosed with epilepsy in a neurology clinic. Most patients are evaluated in the emergency department (ED), hospital, or by their primary care providers and are diagnosed with epilepsy by these providers.[8] This may be a reflection of the VA healthcare system, in which evaluation by a specialist takes longer than in the private sector and sometimes may not be available. The accuracy of diagnosis is likely to be lower when evaluation occurs in the ED or by a primary care provider. Unfortunately, certain racial groups, including African Americans and Hispanics, are less likely than Caucasians to be evaluated by a neurologist.[8]

The diagnosis of epilepsy is also difficult in the elderly as seizures do not present in the same manner as they do in younger patients.[5] Although complex partial seizures are the most common type of seizures in this age group, their symptoms are unique. Auras and automatisms are much less common in the elderly. More common are episodes of memory lapse, altered mental status, confusional episodes, and syncope. In fact, in the VACS #428, seizures were often misdiagnosed as altered mental status, confusion, blackout spells, memory disturbance, syncope, dizziness, and dementia.[5] Idiopathic generalized epilepsies, not often associated with elderly patients, may also re-emerge after a latent period or de novo. Of course, recognizing these types of seizures is important as the treatment implications are different.

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Yet another challenge in the diagnosis of epilepsy is the frequent occurrence of psychogenic nonepileptic seizures (PNES) in veterans. Whereas PNES are also common in the nonveteran population, there are specific challenges in the VA system. The delay in the diagnosis of PNES was almost 5 times greater in veterans – 12.5 months for civilians and 60.5 months for veterans.[9] Additionally, cumulative AED treatment was 4 times greater for veterans.[9] Thus, whereas seizures are difficult to diagnose in elderly veterans, misdiagnosis is also common. This leads to unnecessary treatment with potentially toxic medications.

Treatment of epilepsy in elderly veterans

In my experience, elderly veterans with epilepsy generally are treated with older AEDs than civilians. This may be because only about 25% of elderly veterans are evaluated and diagnosed with epilepsy by neurologists; the remaining are diagnosed and treated by ED/hospital physicians or primary care providers. It is the non-neurologists who are more likely to prescribe suboptimal AEDs.[8] From the mid 1990s to mid 2000s, the use of phenobarbital and phenytoin decreased slightly and the use of newer AEDs increased slightly in veterans over the age of 66 years. Despite this somewhat encouraging trend, as recently as 2004, phenytoin was used in about 66% of geriatric patients with epilepsy and newer AEDs were used in only 19.8%.[10] This is despite numerous recommendations that older patients should be treated with more benign side effect profile. [5, 11-13] This trend is disconcerting as the elderly are at most risk of typical adverse effects of AEDs like phenobarbital and phenytoin, such as gait ataxia, cognitive dysfunction, and bone loss.

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There are some benefits of using older, well-established AEDs such as phenobarbital, phenytoin, carbamazepine, and valproic acid. These include extensive experience, well-identified adverse events, and multiple formulations, including intravenous ones. In my opinion, however, the potential problems with using older AEDs outweigh these benefits. The problems include multiple drug-drug interactions, nonlinear pharmacokinetics, narrow therapeutic margins, and long-term side effects like osteoporosis. Osteoporosis is a significant problem in older veterans. A recent study demonstrated that 43% of 61- to 80-year-old veterans with epilepsy and 71% of 81- to 85-year-olds had reduced bone mineral density.[14] Additionally, the more AEDs the patients were on, the higher the likelihood of having reduced bone mineral density, with combinations of enzyme-inducing AEDs being the most likely to cause this problem.

As noted above, several authors have suggested that newer AEDs may be better suited for older patients.[5, 11-13] Many of the newer AEDs have linear and predictable pharmacokinetics, may be better tolerated than older AEDs, have multiple dosage forms and formulations, have the potential for fewer drug-drug interactions, and may be effective for conditions other than epilepsy (such as migraine, tremor, bipolar disorder, and others).

These drugs have been used so frequently over the last decade that their adverse effects are now more well defined, recognized, and typically manageable.

One of the best AED comparative trials (the VACS #428) was performed in elderly veterans with newly diagnosed epilepsy and compared lamotrigine, gabapentin, and carbamazepine.[6] The primary outcome measure was retention (combination of efficacy and adverse events) in the trial for 12 months. Early terminations were most common for carbamazepine (64.5%) compared to lamotrigine (44.2%) and gabapentin (51%), both statistically significant versus carbamazepine. Because efficacy of all 3 medications was comparable, the terminations were mostly due to adverse drug reactions, with the highest terminations for adverse events in the carbamazepine group. Adverse events in this group included hyponatremia and hypersensitivity reactions. The authors of this study concluded that "lamotrigine and gabapentin should be considered as initial therapy for older patients with newly diagnosed seizures." Topiramate has also been evaluated in elderly patients.[15] After 7 months, 64% of patients remained seizure free with topiramate treatment. The adverse effects were not unexpected and the most common ones included paraesthesia, dizziness, nausea, and loss of appetite. Levetiracetam has also been noted to be well tolerated in elderly patients.[16] Adverse events noted more often in the elderly compared to the younger patients treated with levetiracetam were headache and tremor. Other new AEDs are also being evaluated in elderly patients as well.

Conclusion

There are many challenges faced by elderly veterans with epilepsy. In many cases, the seizures are subtle and difficult to diagnose. Most patients are diagnosed and treated by non-neurologists, and this is associated with treatment with older, suboptimal AEDs. These AEDs lead to frequent short- and long-term serious adverse events. This is even more unfortunate because, in my opinion, the new AEDs have been tested in older veterans with epilepsy and are equally effective and safer when compared to the older AEDs. Within the last few years, Congress established the Epilepsy Centers of Excellence (ECoE) in the VA system. The ECoE network consists of 16 hospitals arranged as 4 regional ECoEs.

These centers are charged with improving care of veterans with epilepsy; conducting research specific to veterans with epilepsy, especially as it relates to posttraumatic epilepsy/TBI; and training the next generation of epilepsy specialists. The ECoEs have already started to favorably impact the management of epilepsy in the VA system. In the next few years, the ECoEs will be able to provide to veterans of all ages the state-of-the-art epilepsy care that they deserve.

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