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Seizures and Epilepsy in the Elderly: Diagnostic and Treatment Considerations

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Abstract

Purpose of Review The purpose of this review is to highlight important clinical aspects in diagnosis and management of epilepsy in the elderly and to highlight recent literature and its relevance to current practice.

Recent Findings Recent studies have shown that elderly patients are under referred for evaluation to epilepsy monitoring units and for epilepsy surgery, which has been demonstrated to be safe and effective in this population.

Summary The elderly are at increased risk for acute symptomatic seizures and epilepsy. Accurate diagnosis can be challenging in older patients due to limitations in history, atypical symptoms, and medical comorbidities. Inpatient video-EEG monitoring is a valuable tool for the clinician when diagnosis is unclear or patients are unresponsive to medication. Drug resistance rates in the elderly are similar to younger adults with epilepsy, but elderly patients are less likely to be referred for epilepsy monitoring unit admissions and epilepsy surgery, despite evidence of safety and effectiveness.

Keywords Seizures · Epilepsy · Elderly · Geriatric · Epilepsy surgery

Introduction

The elderly population is the fastest growing population group in the world [1]. By 2030, there will be at least 1 billion people aged 65 and older worldwide, with up to 71 million in the USA alone [1, 2]. The elderly, defined for the purposes of this review as those aged 60 and older, are at increased risk for seizures and epilepsy compared to the general population, and seizures are the third most common neurological condition in this demographic, behind only stroke and dementia [3–7]. Appropriate diagnosis and management can be challenging in this heterogeneous group, particularly in the setting of medical comorbidities and age-related changes in metabolism. The consequences of seizure disorders can be severe, with increased morbidity and mortality, along with loss of independence and profound impairment in quality of life.

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Epidemiology

In industrialized nations, elderly adults experience the highest incidence and prevalence of epilepsy among all age groups [7]. Indeed, it has been estimated that among all patients with epilepsy, up to 25% are 60 years of age or older [3]. There is a bimodal distribution in incidence of seizure disorders among age groups, with an initial peak in infancy and then a progressively steep increase beginning in the sixth decade of life [8] (Fig. 1).

Prevalence of epilepsy in the elderly has been found to be double that of younger adults with one study identifying this diagnosis in 1% of people ≥ 60 years and even higher (1.2–1.5%) in people ≥ 75 years [12, 13]. Specific at-risk populations, such as nursing home residents who have higher rates of comorbid conditions associated with epilepsy, including dementia and stroke, have prevalence rates reported as high as 9–12% [14–17].

Clinical Considerations

Because brain injuries caused by stroke, head injury, infections, neoplasms, and metabolic disturbances (hypoglycemia, hyponatremia, uremia) are so common in the elderly, it is not

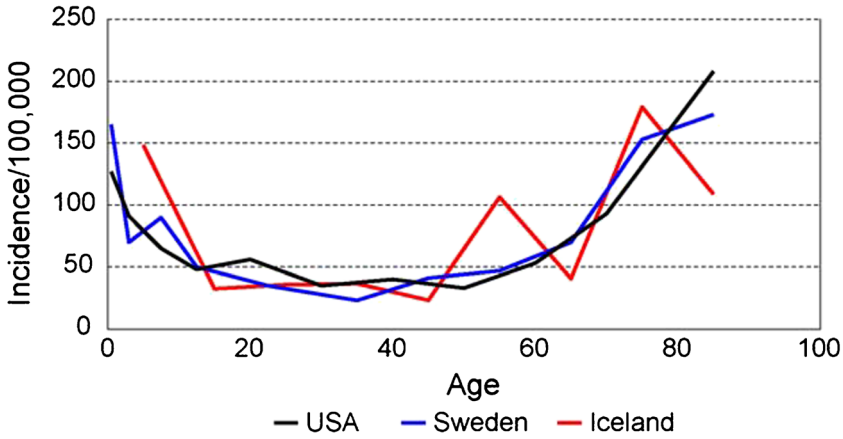

Fig. 1 Incidence of unprovoked seizures through lifespan [5, 9–11]
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surprising that the incidence of provoked seizures (acute symptomatic) is likewise high in this age group [18, 19]. This diagnosis is made in patients in whom seizures occur only in the setting of the acute cerebral insult and do not recur following resolution of the acute illness. Among acute symptomatic seizures, cerebrovascular disease accounts for 40%–50%, metabolic disturbances for 10%–15%, and acute head trauma, brain infections, neoplasms, and toxins/alcohol each account for 5%–10% [4, 19, 20].

Distinct from acute symptomatic seizures, epilepsy is a disorder of the central nervous system characterized by recurrent unprovoked seizures [21, 22]. According to the International League Against Epilepsy (ILAE), a diagnosis of epilepsy can be made if any of the following criteria are met [22]:

- Two or more unprovoked seizures separated by at least 24 h
- One unprovoked seizure and an assessed seizure recurrence risk of at least 60% occurring over the next 10 years
- Diagnosis of any specific epilepsy syndrome

Cerebral insults that can cause acute symptomatic seizure may also lead to subsequent development of recurrent unprovoked seizures and thus a diagnosis of epilepsy. Among these, patients with a history of stroke carry an approximate 20-fold higher risk of developing epilepsy [23]. Dementia and other neurodegenerative conditions are associated with up to 10x the risk for development of epilepsy [5, 18, 19, 24]. In a recent analysis of patients with Alzheimer's disease, dementia with Lewy bodies, and frontotemporal dementia, Beagle et al. found an 11.5% cumulative probability of developing seizures following onset of dementia [17]. The probability was highest in Alzheimer's disease (13.4%) and dementia with Lewy bodies (14.7%) and lowest in frontotemporal dementia (3.0%). Falls with head trauma – particularly common in the elderly – are also risk factors for development of epilepsy [18, 19]. In about 50% of elderly patients, the epilepsy diagnosis is considered to be cryptogenic [5, 20].

Despite the recognized increased risk in the elderly population, correct diagnosis of seizures and epilepsy remains challenging. In a study of patients aged 60 years or older with new onset epilepsy, the average duration from symptom onset to diagnosis was 2.3 years, and only 37% of patients were correctly diagnosed at the time of initial evaluation [25]. Obstacles to appropriate diagnosis in elderly patients include:

- Limited history and lack of accurate descriptions
- Differences in the clinical manifestations of seizures
- High frequency of medical comorbidities, which are often presumed to be the cause of symptoms

A thorough history is critical in establishing an appropriate differential diagnosis for elderly patients with possible seizures. Unfortunately, many older patients live alone and may not be able to provide information about episodes of lapses in awareness or unresponsiveness. Some elderly patients' abilities to communicate are limited by cognitive impairment/dementia or other neurological or physical barriers to speech. With patients who live in nursing homes or have caretakers, unfamiliarity with the patient can impede appropriate history-taking, and effort should be made to contact family or staff members who can provide descriptions based upon direct observation of characteristic episodes.

Clinical manifestations of seizures also may differ in older patients. Because the lesions associated with epilepsy in elderly people can involve any area of the brain, seizures may manifest with a wide variety of sensory, visual, cognitive, and behavioral phenomena that are frequently atypical for the physician's experience and thus more difficult to recognize as having an epileptic basis. Semiology may include more atypical and nonspecific symptoms such as dizziness, confusion, abnormal head sensations, and memory loss [6]. One retrospective analysis identified less frequent focal motor and generalized motor activity in elderly patients [26]. Silveira et al. also noted that compared to younger adults, older patients were less likely to report auras or experience

generalized tonic-clonic seizures and were significantly more likely to report their events as brief episodes of confusion [27].

Comorbid medical conditions can further impede the clinician's ability to make a correct diagnosis of seizures. In patients with coexisting cardiopulmonary disorders, cerebrovascular disease, dementia, and/or renal/hepatic/endocrine dysfunction, episodic symptoms (including falls) are often attributed to these conditions rather than considering a diagnosis of epileptic seizures.

Diagnosis and the Role of Video-EEG Monitoring

Though not every patient with epilepsy warrants EEG monitoring, this may be valuable in clarifying many aspects of diagnosis and management. Several types of EEG testing (routine, ambulatory, inpatient video EEG) are available for the clinician, and it is important that the provider selects the optimal test for the clinical scenario.

"Routine" EEGs (office based, typically 30–40 min recordings) are limited by their short duration and absence of video recording. However, they are low-cost and easy to obtain and repeat. The diagnostic yield of a single routine EEG is notoriously poor, even in patients with epilepsy, capturing abnormalities in only 38.3–50% [28, 29]. This can be increased with repeat testing but improves the yield only up to approximately 60–70% [29].

Ambulatory EEGs (typically 1–3 days of continuous EEG recording) have the benefit of long duration EEG recording, including prolonged recording of sleep, during which epileptiform abnormalities are more likely to be recorded [30]. As ambulatory studies allow the patient's EEG to be recorded outside of the hospital setting, hospital admission-associated complications such as deep venous thromboses can be avoided [31]. These studies also have the theoretical benefit of allowing patients to be recorded during habitual activities in their normal environment, and typical episodes may be more likely to be recorded. Ambulatory studies are limited, however, by frequent contamination of electrode artifacts, lack of consistent quality video correlation, dependence on patient reporting, and absence of neurologic assessment during events. A recent study of elderly patients who underwent ambulatory EEG monitoring identified a diagnostic yield of only 37% [31].

Video EEG (vEEG) monitoring in an inpatient epilepsy monitoring unit (EMU) is the gold standard test for patients in whom a seizure disorder is in the differential diagnosis [32•]. This procedure allows prolonged, continuous EEG and video recording, with monitoring and supervision by trained medical staff who can perform neurologic assessment during and after episodes. EMU admission allows for relatively rapid medication transitions and reduces the serious risks associated with seizures including falls, aspiration, and status epilepticus [32•, 33, 34]. Common indications for EMU admission include [32•, 33–35]:

- Distinction between epileptic seizures and non-epileptic events (physiologic and psychogenic)
- Rapid medication optimization
- Seizure quantification and detection of unrecognized and/or subclinical seizures
- Evaluation for epilepsy surgery

Unfortunately, despite the recognized high prevalence of epilepsy in the elderly and the difficulty in accurately diagnosing seizures in this population, video-EEG monitoring is an underutilized tool in older patients. In a study by Kellinghaus et al., only 3.3% of patients admitted to the EMU were age 60 or older [26]. In a small series of 18 elderly patients admitted for video-EEG monitoring, 5/18 were diagnosed with epileptic seizures, and 10/18 were diagnosed with medical or psychiatric conditions other than epilepsy including normal pressure hydrocephalus and severe depression [36]. Importantly, 8 of these 10 patients *without epilepsy* had been treated with anti-seizure medication prior to definitive diagnosis with video-EEG monitoring. Only 3/18 patients had non-diagnostic admissions. In a larger series of 94 elderly patients admitted for video-EEG monitoring, typical paroxysmal episodes were recorded in 76% (75/99) of admissions [37]. About 49% (46 of 94) of patients were found to have epileptic seizures, and 29% (27/94) were diagnosed with non-epileptic events including symptomatic hypotension, cataplexy, and TIA. The majority of these patients had been inappropriately prescribed anticonvulsant medication prior to correct diagnosis by video-EEG monitoring. These findings underscore the need for video-EEG monitoring in patients whose seizures are atypical and/or have not responded to treatment with anticonvulsant medication. Indeed, video-EEG monitoring may be particularly useful in helping clinicians to discontinue anticonvulsant medication, as these are likely overprescribed in the elderly population. One study found that 10% of nursing home residents have had anti-seizure medications ordered at some point during their admission [16].

Non-Epileptic Spells in the Elderly

Among the advantages of video-EEG monitoring is the ability to diagnose a broad array of medical and neurological conditions other than epilepsy. Given the previously described high frequency of non-epileptic episodes in the elderly, EMU admission can serve as a critical test in patients in whom diagnosis remains uncertain [37]. This section will highlight several common conditions in the elderly that are often misdiagnosed as seizures. (Table 1) Importantly, the provider should recognize that classification of events as non-epileptic

Table 1 Paroxysmal episodes that may mimic seizures in elderly patients

Syncope
Transient global amnesia
Transient ischemic attacks
Complex migraine
Tremor
Myoclonus
Confusional episodes due to medication interactions or overmedication
Hypoglycemia
Electrolyte disturbances/dehydration
REM behavior disorder
Non-epileptic psychogenic seizures

in nature does not necessarily signify the event as psychogenic, also described in further detail below.

Cardiovascular conditions, including convulsive syncope, cardiac arrhythmias, and autonomic dysfunction, are relatively common in the elderly. These disorders can manifest as episodic loss of consciousness with transient limb movements and are frequently misdiagnosed and treated as seizures [38, 39]. With single lead EKG on all patients and the possibility of cardiac telemetry monitoring, inpatient video-EEG monitoring allows for capture of target events with correlation to EEG for definitive diagnosis.

Sleep disorders and parasomnias are also commonly misdiagnosed as epilepsy [39]. REM sleep behavior disorder (RBD) is a relatively common sleep disorder in the elderly, with an estimated prevalence of up to 7.7% [40]. Episodes are characterized by abnormal vocalization and/or movements during sleep, often causing injury to the patient or bedpartner, and like epileptic seizures, patients are amnesic for the events. Early diagnosis is important, as RBD may be associated with an underlying neurodegenerative disorder (i.e., Parkinson's disease, Lewy body dementia, and multiple system atrophy). Hypnic jerks, sleepwalking, and other sleep disorders can also cause transient symptoms without awareness [38, 39]. Video-EEG monitoring can help diagnose these conditions with identification of sleep stage, muscle tone, and absence of electrographic seizure activity on EEG during typical events.

Other neurologic conditions frequently misdiagnosed as seizures in the elderly include TIA/stroke, transient global amnesia, tremor/movement disorders, including dementia with Lewy bodies, as well as complex migraines among others [38, 39]. Complex migraines are associated with focal neurological symptoms, rarely including loss of awareness and confusion in addition to headaches. Transient global amnesia (TGA) is a discrete episode of anterograde amnesia lasting several hours without clear association to epilepsy. TIA and stroke are acute vascular events which can cause focal neurologic deficits and may require emergent evaluation and treatment. Tremor and other movement disorders like tics, myoclonus, and dystonia are also stereotyped behaviors that can be confused with epileptic seizures. Systemic toxic and metabolic disturbances including hypoglycemia, electrolyte abnormalities, and medication side effects can also cause transient neurological symptoms including confusion, diminished responsiveness, loss of consciousness, or rarely focal neurologic symptoms which can be mistaken for seizures.

Psychogenic Non-Epileptic Seizures

Psychogenic non-epileptic seizures (PNES) consist of recurrent episodes of transient neurological symptoms that mimic epileptic seizures but are psychological in nature and not due to abnormal neurophysiological changes in the brain [41, 42]. This is a relatively common diagnosis among all patients referred for video-EEG monitoring, comprising 25–30% of EMU admissions [35]. Elderly patients may have a slightly lower incidence of PNES, with McBride et al. diagnosing 14% of older patients admitted to the EMU [37]. Interestingly, Duncan et al. identified that older patients with PNES (age greater than 55 years) were more likely to be male, more likely to have more significant medical comorbidities, more likely to report healthcare-related psychological trauma, and less likely to report a history of sexual abuse [43]. No difference in semiology was identified between elderly patients and the general adult population. Treatment for PNES consists of individual psychotherapy with a mental health provider experienced in treating the condition. Anti-seizure medications are not indicated and may indeed be harmful to the patient, particularly in the elderly population given the frequency of medical comorbidities.

Treatment Considerations

The decision to begin anticonvulsant medication in an elderly patient who has experienced a single seizure can be difficult; several factors are involved, including assessment for underlying provoking factors, neuroimaging results, neurophysiologic testing results, and potential consequences of recurrent seizures. In the general population, the 2-year recurrence risk following a first unprovoked seizure is approximately 38%, and as such, treatment is not recommended for all patients following a first unprovoked seizure [44, 45]. However, as new-onset unprovoked seizures in the elderly are more often associated with an identifiable underlying etiology such as cerebrovascular disease, there is likely a higher risk of seizure recurrence in this age group [6, 18]. Thus, following a confirmed epileptic seizure, once reversible provoking factors have been excluded as a cause, it is reasonable to initiate anticonvulsant medication in an elderly patient even in the absence of an underlying demonstrable neuroimaging or EEG abnormality [6]. Mortality among older adults with

definite epilepsy may be up to three times that of the general elderly population, and elderly adults with epilepsy are at increased risk for morbidities associated with epileptic seizures, including falls, fractures, and status epilepticus [46–48]. Appropriate treatment of epilepsy can reduce the risk of seizure-related morbidities, reduce mortality, and overall improve quality of life.

Complexities of Medical Management

While elderly patients represent a truly heterogeneous population, some generalizations can be made with regard to anti-seizure medication. As the population ages, several key changes occur as related to physiology and drug metabolism. Elderly patients have a greater proportion of body fat, reduced renal clearance, decreased hepatic blood flow and clearance, impaired medication absorption, and reduced protein binding; all of these can affect drug levels and increase the risk of serious medication associated adverse effects.

Numerous medications have been described to have a markedly reduced clearance in the elderly, including levetiracetam, lamotrigine, gabapentin, lacosamide, and topiramate, among others [47, 49]. The prevalence of medical comorbidities in these patients exacerbates both the frequency and severity of adverse effects from medications. Further, high rates of polypharmacy in the elderly population add significant risk of drug-drug interactions and alterations in hepatic metabolism. The caveat "start low and go slow" is strongly recommended as a basic principle in treating elderly patients with any anti-seizure medication – initial dosing should be lower than with younger adults, and titration schedule should be slower [50].

In general, newer generation anticonvulsants (including lamotrigine, gabapentin, levetiracetam, and zonisamide, among others) are preferred to older generation anticonvulsants (phenytoin, phenobarbital, primidone, valproate, and carbamazepine) in the elderly due to better tolerability and reduced drug interactions, with no difference in efficacy between the two groups [51–53]. A recent randomized, double-blinded clinical trial comparing efficacy and tolerability of controlled-release carbamazepine, levetiracetam, and lamotrigine was performed in 361 patients aged 60 or older [50]. This study found that a significantly higher percentage of patients discontinued carbamazepine due to adverse effects by week 58 of the study, suggesting superior tolerability of levetiracetam. There was no significant difference in tolerability of lamotrigine or seizure-freedom rates between groups. A detailed review of the available literature was summarized in the 2018 AAN Practice Guideline Update Summary on the Efficacy and Tolerability of the new antiepileptic drugs [52, 53].

Elderly patients with epilepsy on anticonvulsant medications are at high risk for bone-related disease including osteopenia, osteoporosis, and fractures [48, 54]. In addition to increased risk of falls due to epilepsy and medication side effects, numerous anti-seizure medications contribute to bone mineral density loss including phenytoin, carbamazepine, oxcarbazepine, primidone, and phenobarbital [47, 48]. Risk of osteoporosis in patients with epilepsy can be reduced with behavioral modifications (exposure to sunlight, weight-bearing exercise, smoking and alcohol cessation, proper nutrition) and supplementation of vitamin D and calcium. DXA scanning should be considered in patients on chronic enzyme-inducing anticonvulsant medications or valproic acid [48].

Efficacy of Anticonvulsant Medications

Anticonvulsant drug resistance rates in the elderly are similar to those in the adult population at large [55, 56]. In a randomized trial that compared response in the elderly to treatment regimens using carbamazepine (dosage range 200–800 mg daily) and lamotrigine (dosage range 75–300 mg daily), Brodie et al. found that only 33% remained seizure free during the final 16 weeks of the study [55]. Similarly, in a study of US veterans, randomizing elderly patients with new onset epilepsy to treatment with gabapentin, lamotrigine, or carbamazepine, only 53% of patients who remained on treatment were seizure free at 12 months [56]. These findings are similar to seizure control rates in the general population, illustrated by Kwan and Brodie's study of 470 previously untreated patients with epilepsy; 47% of patients became seizure free on the first drug, and a total of 61% became seizure free with the second or third monotherapy agent [57].

Epilepsy Surgery

While the majority of patients with epilepsy will be controlled with one or two anti-seizure medications, patients who are not seizure free should be considered for epilepsy surgery evaluation [58]. Resective epilepsy surgery is superior to continued medication trials in patients with drug-resistant focal epilepsy [58]. Unfortunately, older adults with epilepsy are clearly under referred for epilepsy surgery; while approximately 25% of patients with epilepsy are aged 60 years or older, and roughly 1 in 3 patients with epilepsy will be drug-resistant, one study identified that only 12% of all adults undergoing epilepsy surgery were aged 50 years or older [59•].

Data on the efficacy of epilepsy surgery in elderly patients suggest similar seizure freedom and complication rates compared to younger adults [59•, 60, 61]. Grivas et al. published on the outcome of temporal lobe resection in 52 patients older than 50 years (range 50–71, mean 56) [60]. At follow-up of at least 12 months (mean duration 33 months), 71% remained seizure free, virtually identical to that seen in a comparable cohort of 321 patients under 50 years of age (72% seizure free)

undergoing resective surgery in the same time period. Notably, 11 of the 52 patients were older than 60, and outcome was equally good in this subgroup. Only 1 patient showed no improvement in postoperative seizure control. Surgical complications were somewhat higher (7.7%) in this older cohort, and there was also a higher rate (3.8%, 2 patients) of permanent mild neurologic morbidity, compared to younger patients. No patient had severe permanent neurologic morbidity, and there were no mortalities.

In a prospective longitudinal study from 1990 to 2009 in Sweden, Bialek et al. assessed outcomes after resective epilepsy surgery in 558 patients [59•]. About 67 patients (12%) were ≥ 50 years of age, and at the 2-year follow-up point, 61% of patients were seizure free, equal in comparison to group ranging 19–49 years of age. Further, there was no difference between the two groups with regard to the occurrence of major complications (3% in both groups).

Similarly, Dewar et al. reported outcomes following resective epilepsy surgery in a relatively small series of 12 patients ≥ 60 years [61]. With at least 1-year follow-up, 6 patients were seizure free, 2 patients were free of disabling seizures, 1 patient had a few early seizures followed by seizure freedom, and 2 patients reported rare disabling seizures; in total 11 of the 12 patients had a good surgical outcome. Further, there was no difference in complication rates in comparison to the younger cohort, despite the majority of the older patients having at least one medical comorbidity. The authors found that 8 of the patients reported excellent satisfaction following the epilepsy surgery and 5 patients reported overall improvements in health. Importantly, the authors concluded that advancing age should not prohibit the consideration of potentially curative epilepsy surgery.

With the recent development of minimally invasive treatments such as MR-guided stereotactic laser ablation (interstitial thermal therapy), there is optimism for further advancement in surgical treatment for refractory epilepsy. Indeed, preliminary results are promising, with superior neurocognitive outcomes, shorter hospital stays, and reduced recovery time [62, 63•, 64]. In the series published by Youngerman et al., 30 patients with refractory epilepsy underwent mesial temporal ablation procedures; 6 of these patients were 60 or older (range 60–69) [63•]. Of these 6 patients, 4 (66%) were seizure free at the 1-year outcome, comparing favorably to the 24 younger patients, of whom 12 (50%) were seizure free. These less invasive approaches may prove to be especially valuable in older patients, who may be at risk for complications associated with more prolonged complex surgical procedures.

Data on more recently approved brain stimulation-based epilepsy treatments such as responsive neurostimulation (RNS) and deep brain stimulation (DBS) in the elderly population are quite limited. As these therapies have proven to be safe and effective in younger adults, it is likely that these will have a role in the elderly population, particularly in patients who are not ideal candidates for resective epilepsy surgery [65, 66].

Conclusion

The elderly represent a rapidly growing, diverse group of patients who are at relatively high risk of seizures in comparison to the general population. Despite the high incidence and prevalence, there is evidence that this group is under referred for evaluation in epilepsy monitoring units. Appropriate diagnosis and management can be challenging due to limitations in history, atypical symptoms, and complex medical comorbidities. The elderly are at higher risk for complications from seizures and medical treatments, so providers should have a low threshold for referral to a tertiary epilepsy center. Selected patients may benefit from epilepsy surgery which is effective and well tolerated in the elderly population.

Compliance with Ethical Standards

Conflict of Interest Christopher J. Elder and Anil Mendiratta each declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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