Considerations in the Management of Epilepsy in the Elderly

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Management of epilepsy in an elderly person requires accurate classification of seizures, a sufficient neurologic assessment to define etiology, and awareness of the patient’s health and social situation. Treatment with an antiepileptic drug requires an understanding of the general health of the patient and the nature of all medications being given to the patient by other physicians. Effective communication with the patient, spouse, any adult children or other caregivers aims to ensure that all understand the goals of treatment, medication side effects and monitoring methods. Concomitant illness such as neurological, psychiatric, metabolic or cardiac disorders will require individualization of treatment plans.

Key words: epilepsy, elderly, differential diagnosis, management.

Introduction

Epilepsy in the elderly will continue to be an important topic for geriatricians and general physicians as its prevalence will inexorably augment, as will the need to make appropriate diagnostic and management decisions. Both the prevalence and incidence of epilepsy increase with age. Hauser and Kurland found a prevalence increase from 7.3 per 1,000 at ages 40–59 years to 10.2 per 1,000 in those older than 60 years. Their study also found the annual incidence per 100,000 to climb from 11.9 at 40–59 years to 82.0 at 60 plus years. Incidence climbs to over 100 at age 80. Combined with an aging population, these epidemiological data establish epilepsy as an increasingly prominent health care issue.

Some Clinical Ictal Manifestations Characteristic of the Elderly

Temporal lobe (dyscognitive) seizures are the most common, followed in incidence by generalised tonic-clonic and focal sensory-motor tonic-clonic attacks.

Temporal lobe seizures may lack clinical manifestations normally seen at younger ages, such as oroalimentary and limb automatisms. An aura may be described as “dizziness” and the attacks may consist of staring, decreased mentation, unresponsiveness or episodes simply termed “blackout spells”.

Gathering accurate seizure descriptions may be more difficult among elderly patients. Memory loss and preoccupation with other medical or psychiatric illnesses may impair recall, while about one-third of patients are simply unaware of their seizures. Because social isolation is more common among the elderly who are retired, not socially active or who live alone, many spells will remain unwitnessed.

Non-convulsive Status Epilepticus

Non-convulsive status epilepticus (NCSE) has been defined as a behavioural or cognitive change from baseline for at least 30 minutes with electroencephalographic (EEG) evidence of ictal activity. The EEG component of this definition consists of continuous or recurrent ictal activity for at least 30 minutes without improvement or return to pre-ictal pattern. There are three principal subtypes: absence, dyscognitive (temporal lobe) and electrographic status epilepticus in an obtunded or comatose patient.

Absence consists of waxing and waning impaired responsiveness to the environment or confusion lasting hours or days in an otherwise neurologically healthy individual. Mild facial myoclonus, blinking and automatisms may occur. Benzodiazepine withdrawal may precipitate some events. The EEG characteristics are 2–3 Hz and bilaterally synchronous spike-wave discharges. An intravenous antiepileptic drug (AED), particularly a benzodiazepine, may resolve both clinical and EEG features.

Dyscognitive (temporal) NCSE overlaps considerably in its manifestation with the absence type. A waxing and waning impaired responsiveness may occur with occasional bizarre behaviour, confusion and automatisms. Moderately persistent ictal activity predominates or is confined to one or both temporal lobes.

Electrographic status epileptics, also known as subtle NCSE, occurs among patients with a severe encephalopathy due to anoxia or sepsis. Awareness may range from confusion to coma, and the EEG consists of polyspike or spike-wave discharges. Subtle motor manifestations, such as minor facial or limb myoclonus, contribute to the impaired awareness. Irregular nystagmoid ocular movements may appear.

Etiology

Stroke is the leading cause of new-onset epilepsy after age 65 years, accounting for 33–55% of cases. Hemorrhagic strokes are the most likely to cause acute or chronic epilepsy followed by embolic events, with thrombotic strokes being the least likely. Major risk factors for development of post-stroke epilepsy are cortical involvement, occurrence of seizures within two weeks of stroke and lobar hematomas.

Primary or secondary brain tumours may present as seizures in this age group but will occur slightly less commonly than in middle age. Cryptogenic seizures in an otherwise healthy elderly person may represent a primary tumour such as a meningioma or a metastatic brain
lesion. Patients with advanced Alzheimer disease may develop seizures, but epilepsy would be a very unusual presenting feature. Degenerative disorders usually cause generalised epilepsy as myoclonic or generalised tonic-clonic attacks. A previous anoxic insult may also produce a generalised seizure disorder.

Metabolic causes should be considered, particularly hypoglycemia. Drugs such as bupropion, clomipramine and selective serotonin re-uptake inhibitors such as fluoxetine can lower the seizure threshold if they cause hyponatremia. Fluoxetine is used infrequently in the elderly as it is heavily protein bound and has significant P450 enzyme effects. Phenothiazines at substantial doses also may precipitate seizures, but other antipsychotics have less effect of this nature.

**Differential Diagnosis**

Just as stroke causes more elderly-onset epileptic seizures than any other condition, other vascular-related symptoms constitute the principal differential diagnostic entities.

**Transient Ischemic Attacks and Other Reductions in Cerebral Blood Flow**

Consisting of “negative” symptoms lasting from 5–10 minutes to about one hour, transient ischemic attacks (TIAs) consist of unilateral somatosensory attacks involving arm and face without a “march”, occasionally with weakness of these areas. Rare, involuntary coarse waverings or trembling movements may occur, but focal clonic or tonic events do not appear. Headache occurs more commonly with TIAs than with focal seizures (Table 1).

Paroxysmal tachycardia, conduction block and other cardiac arrhythmias may produce transient lightheadedness, impaired concentration and even fear. Only rarely do temporal lobe seizures produce ictal arrhythmias. Dislodgement or dysfunction of a pacemaker electrode could produce rhythmic contractions of the diaphragm, thoracic, shoulder or leg muscles and possibly positional-related nausea or unsteadiness.

**Drop Attacks**

Drop attacks in the elderly consist of sudden falling, often while walking, due to a transient quadriparese which clears promptly without neurological deficit. Postural hypotension may be suspected if these occur upon assuming an erect position. Facial pallor, visual blurring or amaurosis and even bilateral myoclonus may accompany syncope.

Transient ischemia of the descending motor pathways in the lower brainstem and upper cervical cord is a possible mechanism but this has never been demonstrated and is not included in lists of TIA syndromes. However, a TIA of the vertebral-basilar system could transiently produce bilateral numbness and weakness of face and limbs. Most patients with such sudden falls do not report other symptoms of vertebral-basilar transient ischemia, such as dizziness, diplopia, ataxia, veering to one side, blurred or darkened vision, dysarthria or unilateral long tract involvement. Cervical spondylosis or a foramen magnum lesion also could produce sudden falls, in rare circumstances.

**Transient Global Amnesia**

This memory disorder occurs in middle-aged and elderly persons and consists of a sudden confusion and bewilderment that may last for several hours and which gradually recedes. The patient remains alert and personal identification and language are intact. Although the patient will not remember the ictus or its events, memory functions otherwise remain intact. Recurrences at widely scattered intervals may occur in 20–25% of patients. Its pathophysiology is unknown.

**Episodic Microsleep**

Several factors could produce episodic impaired awareness, decreased responsiveness and confusion. Episodic diurnal “microsleep” lasting seconds or 1–2 minutes may be signaled by only impaired concentration, decreased performance, staring or even irritability. More pronounced episodes may resemble temporal lobe seizures as they may contain semi-automatic actions in addition to staring, lapses of attention or confusion. Prior to these, the patient may feel fatigued and acknowledge that he or she is sleepy. An afferent stimulus will instantly alert the patient from such an episode. Such attacks may afflict the elderly whose sleep may be impaired by factors such as medication, obstructive sleep apnea or dementia. A lack of REM sleep could produce visual or tactile hallucinations.

**Metabolic Abnormalities**

Transient metabolic derangements such as hypoglycemia, hyperglycemia and hyponatremia could cloud consciousness and even

### Table 1

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<thead>
<tr>
<th>Sensory-Motor Seizures</th>
<th>Transient Ischemic Attacks</th>
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</thead>
<tbody>
<tr>
<td>Focal sensory</td>
<td>&quot;March&quot; possibly</td>
</tr>
<tr>
<td>Focal motor</td>
<td>Clonic or tonic &quot;March&quot; possible</td>
</tr>
<tr>
<td>Location</td>
<td>Face, hand, arm or leg</td>
</tr>
<tr>
<td>Headache</td>
<td>Rare</td>
</tr>
<tr>
<td>Duration</td>
<td>0.5–2 minutes</td>
</tr>
<tr>
<td></td>
<td>2–5 minutes, rarely &gt; 30 minutes</td>
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</tbody>
</table>

"March" = topological progression of symptom or sign.
produce focal or generalised seizures. Simple dehydration among elderly with inappropriate daily health care routines could alter mental state. Several types of alcohol or drug-related episodes could occur in the elderly as well as at other ages.23

Postictal State
Unobserved single or sequential generalised tonic-clonic seizures could produce disorientation, inappropriate idea sequencing or other cognitive impairments.

Psychogenic Seizures
Although we have seen psychogenic seizures in elderly persons with somatoform disorders, this clinical phenomenon occurs rarely in the elderly and must be diagnosed with appropriate in-hospital video telemetry and clinical psychological evaluation.

Psychiatric Aspects of Epilepsy in the Elderly
Depression occurs in almost three-fourths of patients with epilepsy.20 The highest suicide risk in the general population is the elderly male.21 Moreover, among all patients with epilepsy, the estimated risk of death by suicide is four to five times higher than that for the general population.22 Therefore, AEDs that may aggravate depression, such as barbiturates, should be avoided. Because AED overdose is a common suicide method, prescribe small pill quantities and assure that hoarding does not occur. Repeated bouts of delirium of any causation including epilepsy may, in the course of time, uncover or aggravate a dementing state. This will inevitably worsen compliance. Behavioural alterations such as psychosis, restlessness, insomnia, anxiety and aggression may appear postictally.23 Some symptoms may improve with a generalised tonic-clonic seizure—akin to the benefits of electroconvulsive therapy (ECT).

Management
Impediments to optimal epilepsy management that are encountered in other age groups may be accentuated among the elderly. Forgetfulness, disorganisation and motor and visual limitations can impede compliance. Depression and rejection of the diagnosis of epilepsy constitute additional hurdles. One study reviewed by Scheuer disclosed that patients older than 75 years take an average of three types of medication daily, in addition to any AEDs.24 These factors require a relatively simplified antiepileptic dosing regime, made pharmacologically possible by the long half-lives of currently used AEDs. The support of a homecare nurse and the use of a pill box may improve AED compliance.

Elderly patients with epilepsy can usually be classified into one of two groups: relatively healthy persons, and those with multiple medical problems. Drug interactions, greater likelihood of cognitive impairment and complex dosage schedules complicate management of this second group.

Should Single or Rare Seizures Be Treated?
Two aspects should be evaluated in patients with single or rare seizures: the likelihood of recurrence, and the potential for seizure-related injury.

Factors suggesting that treatment could be deferred include: an avoidable or distinctly unusual seizure-precipitating factor, such as a temporary illness, sleep loss, unusual stress, anxiety or grief; or the presence of a dispensable drug known to lower the seizure threshold (Table 2). A relatively short seizure that does not threaten injury would be an additional consideration. A normal or only minimally abnormal EEG without epileptiform activity, and the lack of any clinical or laboratory evidence of a central nervous system cortical lesion, are other aspects diminishing the likelihood of seizure recurrence. Treatment could be withheld when the patient is otherwise neurologically and systemically healthy.

Treatment would more likely be instituted after a first seizure if the attack occurred spontaneously, was prolonged and risked significant injury. Patients with multiple medical problems, and those with clinical or laboratory evidence of systemic or central nervous system illness, are more likely to have seizure recurrence. Such patients and those who live alone are more likely to require treatment. Unfortunately, as indicated above, the therapeutic regime of patients in this category may already be complex and so drug interactions become more likely.25

<table>
<thead>
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<th>Table 2</th>
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<tr>
<td>Factors Influencing Single Seizure Management</td>
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<table>
<thead>
<tr>
<th>Factor</th>
<th>AED Withheld</th>
<th>AED Prescribed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumstance</td>
<td>Avoidable or unusual precipitant</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>Duration</td>
<td>&lt; 5 minutes</td>
<td>&gt; 5 minutes</td>
</tr>
<tr>
<td>Semiology</td>
<td>Focal non-motor or motor awareness retained</td>
<td>Generalised motor Awareness impaired</td>
</tr>
<tr>
<td>General health</td>
<td>Otherwise healthy</td>
<td>Multiple medical problems</td>
</tr>
<tr>
<td>Neurological examination and functional enquiry*</td>
<td>Normal for age</td>
<td>Focal deficit</td>
</tr>
<tr>
<td>EEG</td>
<td>No or rare epileptiform activity; other abnormalities absent or sparse</td>
<td>Moderate epileptiform activity; moderate to severe focal abnormality</td>
</tr>
<tr>
<td>Imaging</td>
<td>Normal; non-focal or sub-cortical abnormality</td>
<td>Focal cortical abnormality</td>
</tr>
</tbody>
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*Review of systems
AED=antiepileptic drug
Common Side Effects of AEDs
Fatigue is the most common side effect of many antiepileptic drugs, although most fatigued patients do not spontaneously mention this symptom. AEDs may impair sleep quality, producing somnolence, impaired cognition and irritability. Most side effects are dose-related and two AEDs in the laboratory “therapeutic range” may well produce such effects. A slight dose reduction may bring significant benefit. Enzyme inducers may reduce bone density, which can be counteracted by vitamin D and calcium supplementation.

Clinical Pharmacology of AEDs
Decline in serum albumin is slight and will unlikely be of clinical significance among healthy elderly persons, but may be considerably significant among those with multiple medical problems. This and a reduction in liver volume and blood flow are the age-related changes that exert the greatest effect upon AED pharmacokinetics. As serum albumin levels decline, drug binding may decrease; this may lower the total serum drug concentration while the unbound concentration remains unchanged. This effect is principally pronounced among highly protein-bound drugs such as phenytoin, valproate and carbamazepine. Alternatively, age-related reduction in intrinsic clearance would tend to increase unbound serum drug concentration. The free fraction of any AED is the physiologically active component and, therefore, that portion responsible for any toxicity. Active clearance of a drug metabolite may decrease and therefore increase the unbound metabolite concentration even though the parent drug may remain stable. This may produce side effects in the presence of normal concentrations of the parent drug. As age-related changes in protein binding and intrinsic clearance can exert variable effects on drug levels and their active metabolites, measurement of serum albumin along with free and total AED concentrations in serum may assist in dosing.

Alpha1-acid glycoprotein (AAG) increases with age and with several illnesses, increasing the protein binding of weakly alkaline and neutral drugs, such as carbamazepine and its pharmacologically-active epoxide metabolite, causing higher total serum drug and metabolite concentrations. However, AAG would not alter unbound carbamazepine levels.

As renal function may gradually decline with age, serum levels of drugs for which a significant fraction is secreted by the kidneys may increase; this includes topiramate, ethosuximide, primidone and phenobarbital. Calcium-containing antacid drugs may reduce absorption of some AEDs, such as phenytoin.

Specific Pharmacokinetic Alterations
Phenytoin (Dilantin): As phenytoin is approximately 90% bound to serum albumin, any decrease in the latter would tend to increase the unbound portion. This could increase clearance but phenytoin metabolism may become saturated at lower serum levels in the elderly, tending to increase its total and free fraction. As the saturable metabolism property of phenytoin causes a disproportionate rise in its levels with dose increases at approximately the mid-therapeutic range, the foregoing considerations suggest that the usual 5mg/kg dosage should be reduced to about 3mg/kg for the elderly. Signs of clinical toxicity and free fraction (unbound) serum levels should be monitored.

In emergent situations, intravenous phenytoin should be given very slowly, as arrhythmias and hypotension are more likely to be produced among fragile elderly, particularly those with multiple medical problems.

Carbamazepine (Tegretol): Carbamazepine clearance may also decrease with age which would extend its half-life from its usual 16–24 hours. Whether the usual auto-induction of carbamazepine persists to lower the half-life is not yet clear. Serum sodium levels may decline in the elderly. Carbamazepine may aggravate or provoke cardiac arrhythmias if there are underlying cardiac conduction disorders; a baseline electrocardiogram would be prudent in an elderly person. It may be necessary to gradually introduce carbamazepine therapy, taking seven to 14 days to arrive at an initial plateau.

Valproate (Epival): The unbound valproate fraction may increase to 10% from the usual 6% of younger patients as the clearance may be less among the elderly. These factors increase the half-life to 15 hours in elderly patients compared to the usual seven hours. Confused patients may forget that after-meals dosing is necessary to avoid gastric irritation.

Topiramate (Topamax): Topiramate and phenytoin are the AEDs most effective for intractable seizure disorders. The topiramate dose should be limited to about 150–200mg/day to avoid fatigue, weight loss, psychomotor slowing, somnolence and dizziness. Begin at 25mg/day and increase slowly. Because 80% of topiramate is excreted by the kidney, the dose must be reduced if renal function is impaired.

Drug Interactions
Antiepileptic monotherapy will diminish side effects, drug interactions and facilitate evaluation of drug performance. This principle, true for all ages, applies principally to the elderly among whom the complexities of polypharmacy are common. Several commonly used medications may inhibit AED metabolism by the P450 hepatic system, including: propoxyphene, erythromycin, cimetidine, diltiazem, fluoxetine, paroxetine, verapamil, valproate and alcohol acutely. Agents that induce AED and other metabolism include phenytoin, carbamazepine, barbiturates, chronic alcohol and nicotine.

Conclusion
Although diagnostic and therapeutic pitfalls are plentiful, most seizure disorders in the elderly respond to judicious management. Frequent follow-up visits with medication review and AED serum monitoring are essential.

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References