EPILEPSY IN THE ELDERLY- SPECIAL CONSIDERATIONS

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Incidence and prevalence:
The incidence and prevalence of epilepsy is higher in the >60 year old population The lifetime risk for epilepsy under the age of 50 is 1.6%, and 3.4 % up to an age of 80. For more details about prevalence and incidence please see table 1. The elderly population with epilepsy can be divided into the healthy elderly besides epilepsy, the elderly population with co-morbidities which includes the nursing home population with epilepsy[1]. Epilepsy associated with stroke and dementia had an inverse relationship with age in nursing home residents[2].

	Incidence	Prevalence	%
General population	0.67/1000	2.4-6.8/1000	
Elderly	2.4/1000	10.8/1000	
Nursing Home	16/1000	60/1000	
Nursing home residents on AED for seizures			7.7%
Seizures associated with stroke			8.9%
Epilepsy (recurrent seizures) after stroke			2.5%
Seizures in Alzheimer's disease	4.8/1000		
Subdural hematoma			38%

Table 1: Incidence and prevalence of epilepsy in the elderly and special populations[1,3-5].

Differential diagnosis for seizures in the elderly
As the incidence of epilepsy increases in the elderly so do other diseases. A careful history and confirmation of the diagnosis, if necessary, confirmation with videoEEG monitoring, is recommended. Common differential diagnoses include: vasovagal syncope, cardiogenic syncope, non-epileptic seizures, hypoglycemia, alcohol withdrawal, electrolyte abnormalities, metabolic encephalopathy, behavioral events –especially in dementia, transient global amnesia, transient ischemic attacks. The differentiation between seizure and TIA can be difficult. Especially focal seizures with somatosensory symptoms can be easily mistaken for TIA and vice versa. Non-epileptic seizures can also occur in the elderly and are independent of age[6].

Co-morbidities:
The most common co-morbidities are stroke, Alzheimer's disease, brain tumors and head injury[1].

Stroke: 8.6% of patients with ischemic stroke and 10.6 % with hemorrhagic stroke experience seizures and the risk of seizure is significantly higher with hemorrhagic stroke[7]. A cardioembolic source of an ischemic stroke has a higher likelihood of being associated with seizure than non-cardioembolic etiologies[8]. Treatment with t-Pa does not increase the risk of developing seizures[9]. Besides hemorrhagic etiology, cortical location of the stroke predisposes to seizures. The risk of recurrent seizures is higher if the time between the onset of stroke and seizures is prolonged. 2.5% of patients develop epilepsy after stroke. Clinical seizure manifestations are dependent on location of the stroke. Typically the time between stroke and the onset of epilepsy is about 5-6 month. Subarachnoid hemorrhage is associated with seizures in 4-26%[8]. No specific AED is recommended for post-stroke epilepsy. There is no preventive treatment recommendation to avoid the onset of epilepsy after stroke, although there was an attempt to study levetiracetam in this setting[8].

Alzheimer's disease: Alzheimer's disease is associated with an increased incidence of seizures compared to the general population[5]. Younger age at onset, greater cognitive impairment and history of antipsychotic use predispose to seizures[5]. Cognitive decline seems accelerated in patients with seizures[10]. Epileptic hyperexcitability may lead to greater amyloid deposition[11]. Pathologic changes in animal models of Alzheimer's

are similar to those observed in human temporal lobe epilepsy[11]. Most seizures in Alzheimer's disease are non-convulsive or focal[10]. Silent electrographic epileptic activity is also reported and has been questioned how much it contributes to the cognitive decline. 24 hour monitoring seems more sensitive than routine EEG for detection subclinical seizure activity in Alzheimer's disease[10]. In advanced Alzheimer's disease it can be difficult to distinguish behavioral events from epileptic seizures. Other dementias and Parkinson's are less likely to be associated with epilepsy.

Head injury and subdural hematoma: Subdural hematoma is a common result of head injury in the elderly. Seizures occur in 38% of patients. 16% occur before hematoma evacuation, 24% postoperatively. Poor neurological status, evacuation of the hematoma and anticoagulation are associated with a higher likelihood of seizures[12]. Levetiracetam seems to be better tolerated than phenytoin in this particular setting[13].

Brain tumors: As the incidence of brain tumors increases with age, tumor associated epilepsy also increases. The greatest risk factor for developing epilepsy in low grade tumors is a history of seizure at diagnosis of the tumor[14]. There are significant drug interactions between chemotherapy and AED. Chemotherapy may reduce the levels of AED like phenytoin, carbamazepine and valproate[15]. Vice versa, enzyme inducers may reduce the levels of chemotherapy, while valproate may actually increase the concentration of active metabolites of antineoplastic drugs. Levetiracetam is considered neutral in that regard.

Diabetes: Seizures due to hypoglycemia or hyperglycemia are an important differential diagnosis in the elderly. AEDs that cause further weight gain such as valproate, gabapentin and pregabalin should be given with caution.

<u>AEDs in the elderly:</u>
Clinical trials in the elderly have been scarce due to co-morbidities and compliance. A recent clinical trial compared discontinuation rates of levetiracetam, valproate and carbamazepine. Discontinuation rates were lowest with levetiracetam, while time to first seizure was comparable in all three substances[16]. A similar study compared gabapentin, lamotrigine and carbamazepine, which again confirmed similar efficacy but discontinuation rate was highest with carbamazepine and lowest with lamotrigine[17]. A comparison of levetiracetam, lamotrigine and carbamazepine for new onset epilepsy in the elderly showed the lowest withdrawal rate with levetiracetam, followed by lamotrigine [18]. In conclusion newer AED such as levetiracetam and lamotrigine seem better tolerated in the elderly compared to older AED and may have less interaction with other medications. Efficacy in terms of seizure control seems to be similar in all AED.

When treating the elderly with AED special considerations should include:

1. Decreased P450 activity in the liver: This mainly affects enzyme-inducing AEDs such as phenytoin and carbamazepine.
2. Decreased kidney function and decreased glomerular filtration rate
3. Decreased protein binding
4. Altered gastro-enteral motility and absorption[19]
5. Fluctuations in AEDs without obvious changes in dosing: In a nursing home population large fluctuations of phenytoin levels were noted in some patients[20].

For all the above reasons lower or less frequent dosing should be considered in the elderly[15,21]. In summary, newer AED such as levetiracetam and lamotrigine seem better tolerated than enzyme-inducers in the elderly[15].

Polypharmacy is common in the elderly. Enzyme inducers (phenytoin, carbamazepine, phenobarbital) may interact with warfarin, frequently co-prescribed with AED. The same applies to tricyclic antidepressants, SSRIs and calcium channel blockers. Oxcarbazepine is more likely to cause hyponatremia in the elderly than carbamazepine[21]. Valproate may decrease platelet function and should be used only cautiously in addition to anticoagulation or antiplatelet therapy. Herbal remedies such as St. John's wart and Gingko biloba may interfere with AED metabolism[19,22] and are not infrequently use in this population.

The interactions with psychotropic drugs such as antipsychotics and antidepressants are complex. Enzyme inducers may decrease the effectiveness of antipsychotics. The greater the number of psychotropic medications used the higher the likelihood that they induce seizures[15]. However, the overall risk of antipsychotics to induce seizures is difficult to estimate and not as frequent as commonly assumed. Only clozaril as a second-generation antipsychotic has a clear association with increased seizures[23,24]. The seizure inducing properties of SSRIs are still discussed[25]. Of the antidepressants, wellbutrin stands out as lowering the seizure threshold.

Special Considerations:

Bone health and falls:

Bone heath is generally declining in the elderly and bone loss predisposes to fractures as frequently occurring during seizures. Enzyme inducing AED such as phenytoin and carbamazepine, as well as valproate have been associated with accelerated bone loss, possibly due to interference with Vitamin D metabolism [1]. Therefore the elderly are at higher risk for fractures with seizures and treatment may be initiated earlier to prevent falling. Vitamin D supplementation is recommended with AED use.

Compliance:

Due to memory impairment and visual impairment, compliance with AED can become problematic. Consider not more than twice a day dosing for AED and supervision of AED intake[19].

Nursing home residents:

The incidence of seizures and epilepsy seems very high in the nursing home population with a very high incidence immediately after admission to a nursing home. The question arises whether all of those events are truly epileptic seizures or whether the higher incidence is due to enhanced supervision versus.

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