Epilepsy and Dementia in the Elderly

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Abstract

Epilepsy is a frequent condition in the elderly; however, it remains a relatively understudied condition in older adults with dementia. The diagnosis of a seizure is particularly difficult and is most often based on questions to the caregiver. Epilepsy in dementia has significant consequences on the prognosis of the underlying dementia: it can result in a worsening of cognitive performance, particularly in language, as well as a reduction in autonomy, a greater risk of injury and a higher mortality rate. In this review, management strategies are recommended for the clinician. The presence of pre-existing Alzheimer's disease does not exempt the clinician from ruling out other symptomatic causes of seizures. Anti-epileptic drugs (AED) should be started only after the diagnosis has been clearly established, when the risk of recurrence is high, and with monotherapy whenever possible. Although few data are available, the more recent AED offer significant advantages over the older medications in this context.

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Introduction

Since age is the major risk factor for epilepsy and dementia, both are frequently seen in the elderly. Due to the continuous aging of the population in western countries,

and the resulting large number of elderly patients with dementia, we need to study epilepsy in this population because of its significant impact on daily functioning. Epilepsy, defined as a chronic illness diagnosed after the occurrence of 2 or more unprovoked seizures (seizures which occur without any obvious immediate cause), must be differentiated from acute symptomatic seizures (which are provoked by acute illnesses) in order to avoid confusing the data on dementia. This paper deals with the diagnosis of seizures in elderly people with dementia, proposes how to classify seizures according to the different epileptic syndromes and discusses their different treatment strategies.

Epidemiology of Dementia, Seizures and Epilepsy

Age is a common factor for both epilepsy and dementia. The prevalence of dementia is estimated to be approximately 6–8% after 65 years of age and may rise to 20–30% in subjects older than 85 years in Europe [1–3]. Although Alzheimer's disease (AD) is the most common form of dementia, other causes include, in descending order, vascular disease, Lewy body disease and frontal-lobe dementia [4].

Epileptic seizures are a clinical manifestation resulting from an abnormal and excessive discharge of neurons (International League against Epilepsy Commission Report [5]), which may produce sudden, diverse, transitory symptoms, including altered consciousness and/or motor, sensory or psychiatric events.

Both unprovoked and acute symptomatic seizures are common in the elderly. The incidence of any type of first seizure is 50/100,000 people aged 40–59 years, and increases to 127/100,000 in those older than 60 years [6]. The prevalence steadily increases with age and is estimated to be 5/1,000 between 20 and 50 years, 7/1,000 between 55 and 64 years and 12/1,000 between 85 and 94 years [7]. The 4 most common aetiologies for seizures in the elderly are cerebrovascular disease, toxic and metabolic aetiologies, dementia and brain tumours [7, 8]. In patients with dementia, the incidence of seizures is 5–10 times greater than expected in a reference population. In a review of the literature, Mendez and Lim [9] reported that between 10 and 22% of AD patients have at least 1 unprovoked seizure. Most studies in dementia have retrospectively evaluated the prevalence of epileptic seizures in patients with autopsy-proven AD [10–12]. In a study in a psychiatric population aged >55 years with dementia (most suffering from AD, but some with vascular dementia), McAreavey et al. [13] reported that 9% of the patients had experienced seizures. Although these studies are interesting, they all had various methodological problems, such as particularly small sample sizes in the neuropathological studies, no systematic evaluation of clinical variables, the absence of imaging studies or a selection bias.

Epilepsy is a frequent condition in the elderly [14]. The annual incidence of epilepsy increases from 110/100,000 people between the ages of 65 and 69 to more than 160/100,000 in those over 80 years [15–18]. In subjects aged ≥ 65 years, dementia and other neurodegenerative diseases account for 9–17% of the epilepsies seen in the elderly [6–8, 14, 15, 19–21].

Seizures in Elderly Patients with Dementia: Diagnosis

The diagnoses of seizures and epilepsy may be particularly difficult in elderly patients with dementia. We focussed on AD because it is the most common form of dementia in the elderly, and more data is available on this disease than on any other form of dementia.

In AD generalized seizures are common and presumably generalize secondarily from a partial seizure focus [10, 11, 13]. Complex partial status epilepticus [22] and myoclonus [10], often a late manifestation, have been reported. In older people with dementia, clinicians may mistakenly consider seizure activity (particularly complex partial seizures) to be symptomatic of the underlying dementia. Indeed, partial seizures may result in a decline

in cognitive functions, a worsening in the performance of the activities of daily living and episodes of confusion [23]. It can also produce non-specific symptoms like dizziness, altered mental status or unresponsiveness. The diagnosis of a seizure is essentially a clinical diagnosis based on a reliable history and is more difficult in demented patients since they often remember little of the episode. Accordingly, corroborative evidence from the caregiver or an observer is important. The physical examination should be centred on the medical history and the neurological and cardiovascular systems.

Several types of transient episodes can mimic seizures including syncope, which can be associated with myoclonus, tongue biting and urinary incontinence. Transient global amnesia (TGA) can be confused with seizure activity [24]. TGA is a clinical syndrome characterized by a number of clinical features: a clear-cut anterograde amnesia with no clouding of consciousness or loss of personal identity, the absence of neurological signs or deficit, no features suggesting epilepsy or active epilepsy, no recent head injury, and resolution within 24 h [25]. Cognitive impairment must be limited to amnesia [26]. This particular form of amnesia is sometimes difficult to differentiate from epileptic disorders, particularly epileptic amnesic syndrome (EAS) [27] also called transient epileptic amnesia [28] which represents a particular type of temporal lobe epilepsy. EAS occurs in senile adults with no history of memory impairment. It consists of repetitive and transient memory impairment, which lasts a few minutes following a seizure. It also may be the sole manifestation of a seizure. Amnesia is anterograde, retrograde or both and is sometimes associated with a few behavioural abnormalities (e.g. perplexity), with no memory of the episodes. Interictal memory disturbances are sometimes seen. EAS may be the result of bilateral deep discharges in the hippocampal-mesial temporal lobe regions or may be a postictal phenomenon. The duration (usually 4–6 h in TGA; <1 h in EAS) and number of attacks (repetitive episodes in EAS) may help to distinguish TGA from EAS.

Transient ischaemic attacks, sleep disorders, psychiatric symptoms (e.g. anxiety) and various metabolic and toxic states (hypoglycaemia, hyperglycaemia and adverse drug effects) can also be mistaken for seizures [14, 29]. Some specific features should be kept in mind concerning aging and dementia. Postictal confusion may last for hours, or even days [30]. Focal motor deficits may last for several hours, erroneously suggesting ischaemic stroke, and tongue biting and urinary incontinence may be absent [14]. It is important to look for the use of medications that lower the seizure threshold and may cause acute seizures:

typical and atypical antipsychotics usually prescribed in AD [31], tricyclic antidepressants, theophylline and antibiotics like quinolones. A few seizures have been reported during treatment with cholinesterase inhibitors [32, 33].

Routine investigations should include a complete blood cell count, serum electrolytes, renal and liver functions and an electrocardiogram. Cerebral imaging is also indicated, in addition to a complete neurological examination, and an electro-encephalogram (EEG). An EEG is neither sensitive nor specific, since age-related changes can be difficult to interpret. Nevertheless, the EEG can be useful, although interictal epileptiform abnormalities are less frequently seen in this population than in younger patients [34]. Consequently, the absence of epileptiform abnormalities does not rule out epilepsy [34]. With advancing age, healthy individuals can develop EEG variants with epileptiform morphology, including the slowing of the resting background, an α -rhythm, whereas slow θ - and δ -wave EEG frequencies can increase with age, in both diffuse or focal localizations [14, 34]. Some features can be very difficult to interpret like the subclinical rhythmic EEG discharges of adults, which consist of rhythmic, sharply contoured waveforms that evolve into a sustained 5- to 6-Hz pattern, lasting 40–80 s; they are usually widespread and often maximal over the parietal and posterior temporal regions of the brain. Another diagnostic difficulty can be periodic lateralized epileptiform discharges which are defined as repetitive periodic, focal or hemispheric epileptiform discharges (spikes, spikes and waves, polyspikes, sharp waves) usually recurring every 1 or 2 s. Periodic lateralized epileptiform discharges are non-specific and can be seen in various acute or subacute conditions: Creutzfeldt-Jakob disease, herpes encephalitis, cerebral haemorrhage or stroke [35, 36]. Brain imaging is necessary in cases of new-onset seizures to search for a symptomatic aetiology like stroke, tumour or subdural haemorrhage. However, there are no reliable markers for neurodegenerative disorders [37], and they may be difficult to interpret in the elderly because of age-related changes like diffuse atrophy and periventricular hyperintensities.

A management strategy is important in order to help the clinician decide whether to initiate treatment or not. In the elderly, Loiseau et al. [21] suggested using a classification based around epileptic syndromes, even after a first seizure. The commission on classification and terminology of the International League against Epilepsy [38] has proposed 4 categories of epileptic syndromes in elderly patients: (1) symptomatic localization-related epilepsy – when there are signs or symptoms of a specific anatomical localization (partial seizures, EEG or brain

CT signs of localization); (2) undetermined epilepsy – concerning patients without unequivocal generalized or focal seizures, and without any aetiological factors; (3) isolated, apparently unprovoked, epileptic events – which includes patients with isolated partial or generalized seizures without EEG or CT scan abnormalities, and without aetiological factors; (4) situation-related seizures (also called acute symptomatic seizures) – which can be associated with metabolic disorders or acute injury to the central nervous system.

Some Special Considerations concerning Seizures and Epilepsy in AD

When exactly, during the course of AD, seizures first occur, has not yet been established. According to some authors, seizures occur in the later stages, 6 or more years after the onset of the dementia [11, 33, 39] and the incidence of seizures increases with the severity of the dementia [9, 13, 19]. Other authors have reported seizures at any time during the course of the illness [10], even as early as 3 months after the onset of AD [19]. Additional researchers have found no association between seizures and patient age at the onset of AD, nor between seizures and any prior EEG findings [12]. More recently, Amatniek et al. [40] evaluated the cumulative incidence of AD/seizures and identified co-morbid medical and psychiatric baseline conditions that can influence the risk of an unprovoked seizure in patients with mild AD, who were prospectively followed at 6-month intervals (median follow-up period: nearly 6 years). The cumulative incidence of unprovoked seizures at 7 years was almost 8%. Independent predictors of unprovoked seizures were younger age, African-American ethnic background, severer dementia and focal epileptiform activity on EEG. Considering patient age at onset, seizures are more likely to occur with early-onset disease, particularly in the familial form with the presenilin 1 mutation [41–43].

In AD, the nature of the underlying mechanism for unprovoked seizures remains unclear. The role of the accumulation of amyloid β plaques, neurofibrillary tangles and extensive neuronal cell loss in limbic and association cortices has been suspected [9]. However, compared to AD patients without seizures, AD patients who had seizures were not different with respect to other medical disorders they had, the medications they took or the degree of focal pathology [11, 12]. The role of a disproportionate neuronal degeneration in different brain areas has been postulated to be the neuropathological substrate of sei-

zures in AD [44]. In fact, for 6 patients with generalized motor seizures among 56 with autopsy-proven AD, Forstl et al. [44] reported significantly reduced pyramidal cell counts in the parietal and hippocampal areas. However, cell loss may not be the only pathological basis for seizures in AD. The accumulation of amyloid β plaques may also play a role as is seen in the description of seizures in cases of amyloid- β -related angiitis [45]. Additional evidence for the role of neuropathological lesions comes in reports of seizures in families with early-onset AD associated with presenilin 1 mutations [42, 46]. In fact, a relationship between cell loss in the CA1 field of the hippocampus, a high density of amyloid β plaques and neurofibrillary tangles, and seizures has been postulated in patients with familial AD. Neuronal death may consequently affect GABAergic inhibitory circuits and the balance between excitation and inhibition which may induce seizures [11]. In addition, the description of a possible relationship between neuronal loss, hippocampal atrophy and seizures has been documented by the data concerning hippocampal sclerosis, which is defined as severe neuronal loss and gliosis in the CA1 field and the subiculum of the hippocampus, combined with synaptic reorganization. Although hippocampal sclerosis is the most common abnormal lesion identified in temporal-lobe epilepsy, it has been reported in many different dementias, including AD, dementia with Lewy bodies or frontotemporal dementia [47]. However, in all these cases, no seizures were described. An alternative to the role of anatomopathological lesions could be the selective loss of inhibitory neurons which may facilitate the occurrence of seizures [11]. Seizures can also result from non-AD lesions, like cerebrovascular lesions [48] or metabolic or neurotransmitter disorders [11].

Unprovoked seizures have significant consequences on the prognosis of dementia: aggravation in dementia in terms of a loss of cognitive abilities, reduced autonomy, greater risk of injury and a higher mortality rate [22, 49, 50]. Language functions declined significantly more rapidly in AD patients with seizures than in controls matched by age and duration of AD, and the patients' condition suddenly worsened and required admission to a long-term care facility within 6 months of the seizure onset [50]. A number of different factors can be considered in order to explain this worsening, such as infraclinical epileptiform discharges [51] or associated psychiatric symptoms [52]. Seizures may have serious consequences like falls, fractures, intracranial haemorrhages and long-lasting confusion, which is particularly worrisome in dementia. Finally, patients with dementia are very vulnerable to the negative effects of anti-epileptic drugs (AED) [53, 54].

Seizures and Epilepsy in Non-AD Dementia

The risk of seizure is not limited to AD but there are few data concerning other types of dementia. In a report from the Mayo Clinic (Rochester), other types of dementia, referred to as non-AD dementias, increased the risk of partial seizures 11-fold and the risk of generalized seizures 7-fold [19].

No study to date has examined the incidence of epilepsy in frontotemporal dementia [55]. Recently, Sperfeld et al. [56] reported a novel phenotype characterized by the early onset of rapidly progressive frontotemporal dementia and parkinsonism with epileptic seizures linked to chromosome 17 [57]. Unfortunately, there is no data about the prevalence of epileptic disorders in Lewy body disease.

Some specific conditions which can also associate dementia and seizures must be considered. The clinical presentation of Hashimoto encephalopathy at the onset may be acute (stroke-like episodes, seizures, impaired consciousness) or insidious with dementia and psychosis [58]. Authentic epileptic seizures (primary or secondary generalized seizures) have been reported in Hashimoto encephalopathy patients [58–61], but status epilepticus has only rarely been described [60, 62]. Various EEG abnormalities have also been described and are usually non-specific: diffuse slowing, mesial temporal lobe epileptic foci during ictus, diffuse slowing with triphasic discharges [63]. The pathogenesis of Hashimoto encephalopathy remains unclear but a favourable outcome with glucocorticoid therapy strongly suggests an auto-immune mechanism.

In the initial presentation of sporadic Creutzfeldt-Jakob disease, seizures rarely occur but are often resistant to AED [64, 65]. They can be in the form of *epilepsia partialis continua* [65–67] or generalized convulsive status epilepticus [68]. Depending on the disease stage, the EEG can show non-specific findings such as diffuse slowing and frontal rhythmic δ activity in the early stages, disease-typical periodic sharp wave complexes (lateralized or generalized) or periodic lateralized epileptiform discharges.

Multi-infarct and vascular dementia, also called vascular cognitive impairment [69], may also cause seizures. There is no data on epilepsy in vascular dementia and more studies have addressed post-stroke epilepsy [8, 70]. The overall incidence of cerebrovascular-related seizures is estimated to be between 3.6 and 8.9% [71, 72]. Some authors have individualized predictors of late-onset seizures and epilepsy, like the severity of the initial neurological impairment [72, 73] and the presence of a large

cortical infarct on brain CT scan [72, 74–76]. Repeated seizures following an ischaemic stroke promote vascular cognitive impairment [77]. Pre-existing dementia increases the risk of late seizures after stroke (occurring more than 7 days after stroke) but not of early seizures (occurring within 7 days of stroke onset) [78].

Treatment

Epilepsy, defined as the occurrence of at least 2 unprovoked seizures separated by a greater than 24-hour interval, should be treated. In addition, Loiseau et al. [21] believe that elderly patients who have experienced only 1 seizure at the time of referral, but have a high risk of recurrence, should also receive treatment. However, the decision to treat is difficult because dementia patients often have associated co-morbidities and co-medications and may be more sensitive to adverse effects. Therefore, safe and effective treatment is essential.

Most dementia patients are elderly and are therefore more likely to have pharmacokinetic changes, especially due to AED and their side effects, drug interactions and toxicity due to diminished hepatic and renal functions. There is no specific data available on the treatment of epilepsy in dementia, and no controlled studies have been performed. The best we can do is extrapolate from data concerning elderly people [9]. AED should only be used with the awareness that demented elderly subjects are particularly fragile.

Since AED may cause numerous adverse effects, the clinician should pay particular attention to their occurrence with respect to cognition (mental slowing, confusion) or sedative effects. These consequences are particularly significant in patients with dementia because AED can intensify impairments in memory and other cognitive functions [53]. In fact, demented patients are particularly vulnerable to the cognitive effects of AED [9].

Traditional AED, like phenobarbital and phenytoin, have greater effects on cognition than the more recent AED [79]. They should also be avoided because of the sleepiness and osteomalacia they can produce, and the subsequent major risk of fracture due to loss of balance and ataxia. Phenytoin has other disadvantages in elderly patients, such as effects on liver metabolism, associated enzyme induction and non-linear pharmacokinetics [80]. Carbamazepine may be difficult to use in the elderly because of drug interactions, cardiac side effects, hyponatraemia and sedation. Primidone and benzodiazepines are not recommended because they can worsen cognition

in dementia patients [81]. Valproate has been prescribed in older patients with partial or/and secondary generalized seizures and is usually well tolerated [82]. In addition, it does not induce the metabolism of hepatic enzymes, does not affect the metabolism of vitamin D and is not associated with osteomalacia. Dose-dependant adverse effects include gastro-intestinal symptoms (nausea, vomiting, heartburn, abdominal pain), temporary hair thinning or loss and fine hand tremor [14]. The cognitive effects of valproate were usually considered to be minimal [83]. However, some motor and cognitive (dementia-like) impairments have been associated with valproate use, although all the symptoms disappeared with the discontinuation of the drug [84–87].

New AED give promising results and have fewer side effects upon cognition [79, 88, 89]; however, gabapentin does require 3 doses per day [90]. Lamotrigine has a positive neuropsychological profile [90, 91], but its major adverse effect is the development of rashes that require a progressive increase in dosage. Few data are available concerning topiramate in the elderly; however, the reductions in measures of attention and word fluency described in adults, as well as weight loss, suggest that it should be used with caution [92, 93]. Oxcarbazepine, a derivative of carbamazepine, can also cause hyponatraemia [94], which occurs more frequently in elderly patients. There is still limited experience with the use of levetiracetam in the elderly [93], particularly with dementia.

In spite of the lack of specific data in elderly subjects with dementia, the study of Rowan et al. [95] can help the clinician in choosing an AED. This interesting study consisted of a multicentre clinical trial of seizures in patients aged 65 and older, with newly diagnosed seizures and no restrictions regarding concomitant diseases. Some of the patients had mild cognitive impairment (35%) or memory loss (26%). Lamotrigine and gabapentin were compared to carbamazepine and had comparable efficacy, but patient tolerance was best with lamotrigine, immediately followed by gabapentin. Consequently lamotrigine and gabapentin should be considered as initial therapy for older patients, even when they have a cognitive impairment.

In elderly patients with dementia, the clinician has to consider the cognitive profile of the AED, and treatment should be initiated at low doses and slowly titrated. Monotherapy is recommended whenever possible (table 1) [88].

Drug interactions are more likely to occur in elderly demented patients with co-morbidities who are taking several medications. Among these co-morbidities, psy-

Table 1. Posology of AED in elderly patients with dementia (inspired by Mendez and Lim [9] and Rowan et al. [95])

	Starting dosage mg/day	Dose increment	Target dose (mg/day)	Target dose of Rowan et al. (mg/day)
Carbamazepine	100–200 in 1 or 2 doses	200 mg every 2 weeks	400	600
Valproate	250 in 2 doses	300 mg	800	
Gabapentin	300–400 mg twice daily	300 mg (or 400) every week	1,500	1,500
Lamotrigine	25 with valproate 50 without valproate (during 2 weeks)	50 mg/day during 2 weeks	100–200	150
Oxcarbazepine	600 in 2 doses		900	
Levetiracetam	1,000 in 2 doses	500 mg	1,000–2,000	
Topiramate	25–50	25 mg every 1 or 2 weeks	100–150	

chiatric and behavioural symptoms justify the use of antipsychotic agents in addition to the classical symptomatic treatment with cholinesterase inhibitors or memantine. However, pharmacological therapy with antipsychotic agents may present a problem, since they lower the seizure threshold [96] and their effectiveness has not been clearly established [97]. Depression and anxiety are other common co-morbidities. Treatment needs to take into account the decrease in seizure threshold, which has been reported for some antidepressants and the mood-modifying properties of some AED like valproate, carbamazepine or lamotrigine [98]. The antidepressant which has the lowest tendency to reduce seizure thresholds and with the least potential for altering AED metabolism should be chosen [99]. Among the cardiovascular medications often prescribed, statins play a consistent role because they are metabolized in the liver and may interact with AED [99]. Even if few data are available on elderly patients with dementia, newer AED should be preferred, because they do not affect statin metabolism [96].

Conclusion

With the steady increase in the number of elderly people in the general population, more and more patients will receive a diagnosis of, and be treated for, epilepsy. This constitutes a major public health problem. AD patients have an increased risk for epilepsy, and when both disorders are present, they constitute a complex association with a potentially major psychosocial impact. The diagnosis of epilepsy is difficult and management strategies are recommended for the clinician, even in cases of de-

mentia. A seizure which occurs in a dementia patient may be due to a single event-related metabolic disorder and should not necessarily be treated. After a single seizure, AED should be only started after the diagnosis has been clearly established, and when signs suggesting an anatomical localization are present or when the risk of recurrence is high. Monotherapy should be used whenever possible. AED treatment must be guided by its possible adverse effects and their interaction with concomitant medications often prescribed in geriatric patients with epilepsy. Accordingly, the newer AED seem to offer significant advantages over older medications; however, clinical trials evaluating their use in the elderly are still needed, particularly in dementia. The management of epilepsy in elderly patients with dementia, therefore, requires close collaboration between neurologists and geriatricians.

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