Evaluation of Comorbid Epilepsy and Dementia

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Introduction

Epilepsy and dementia are both commonly occurring neurological disorders. In fact, these disorders fall in the top four most common neurological illnesses, along with migraine and stroke [1]. Alzheimer's disease (AD) is estimated to occur in over five million people across the USA [2] and epilepsy in just under three million individuals [1]. Overall prevalence rates for dementia more broadly are approximately 1–2% at age 65 years and as high as 30% by age 85 [3]. For example, in individuals over 65 years of age, dementias account for up to 17% of epilepsies seen in the elderly [4]. Similarly, the highest incidence of newly diagnosed epilepsy cases occurs over the age of 65 years [5]. The factors playing into their heightened co-occurrence in this age group are not well known. However, it is known that epilepsy in the elderly often presents differently than epilepsy in younger adults, and that symptoms of dementia can be exacerbated by seizures. Due to the high prevalence rates of epilepsy and dementia, it is important for neuropsychologists to understand the bidirectional relationship between dementia and epilepsy.

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Definition of Epilepsy and Seizures

Seizures can be defined as a strong surge of abnormal electrical activity causing an excessive discharge of neurons. This electrical abnormality results in a variety of clinical semiologies that are also accompanied by changes in electroencephalography (EEG). Common seizure semiologies include motor abnormalities (e.g., automatisms, tonic-clonic movements, head deviation, eye deviation), behavioral arrest, reduced cognitive functions, and/or sensory perceptions (e.g., gastric rising, tingling, ringing, changes in vision, taste, and smell). The underlying neuronal abnormality that causes seizures is not fully understood. However, seizures are most likely the results of 1) abnormal cellular membranes resulting in lowered firing thresholds and/or 2) an imbalance between excitatory and inhibitory neurotransmitters.

Epilepsy is broadly defined as a disorder of the brain characterized by a persistent predisposition to epileptic seizures [6]. More specifically, epilepsy is diagnosed when at least two unprovoked seizures occur more than 24 h apart. An unprovoked seizure is one that has no clear antecedent cause. An epilepsy diagnosis can be given following one unprovoked seizure if the probability of further seizures is similar to the general recurrence risk after two unprovoked seizures (at least 60%) [6].

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Seizures can be characterized in a number of ways. Recently, the International League Against Epilepsy (ILAE) revamped the clinical definitions of seizures. Based on 2017 ILAE criteria [6, 7], there are three broad categories of seizures, which include generalized onset, focal onset, and unknown onset. Generalized onset seizures involve the whole brain at the outset of the seizure and can be further characterized by motor or nonmotor (i.e., absence) features. Focal onset seizures begin in a localized area of the brain and are further subcategorized as focal aware or focal impaired awareness seizures. Both aware and impaired awareness focal seizures can be categorized with a motor onset or a nonmotor onset. Additionally, focal onset seizures can generalize to involve the whole brain; these seizures are referred to as focal to bilateral tonic-clonic seizures. Patients can present with multiple seizure types and seizure types can vary throughout the course of an individual's epilepsy. Epilepsy type is categorized into four groups including focal, generalized, combined generalized and focal, and unknown. The term "pharmacoresponsive," which suggests that seizures are controlled by antiepileptic drugs (AEDs), is now to be used when appropriate.

Epilepsy in Patients with Dementia

Cerebrovascular disease accounts for about one-third of newly diagnosed cases of epilepsy in older adults [8]. Other common etiologies for new-onset epilepsy in elderly populations include: toxic and metabolic causes, dementia, and tumors [4] and, less likely, head injury, neurological infection, or drug interactions [9–11]. That being said, approximately 12% of new-onset seizures in elderly patients are attributed to degenerative disorders [8, 12, 13]. Seizures are most common in the advanced stages of AD [14], but early stage onset is also associated with increased risk of seizures [15–17]. Regardless of when in the disease process seizures occur, patients with dementia, particularly AD, have a five- to ten fold increase in risk of seizures [12]. It is estimated that between 10 and 22% of patients with AD will experience at least one seizure [8, 16, 18, 19]. In individuals with dementia, characteristics associated with the disorder may interact with known etiologies of epilepsy. For example, preexisting dementia increases the risk of poststroke epilepsy, [20] and the use of acetylcholinesterase inhibitors for treatment of AD has the potential to elicit increased neuronal hyperactivity [21, 22].

Individuals with epilepsy are at an increased risk for developing dementia as an older adult. One potential reason for this increased risk is that individuals with chronic epilepsy exhibit medical factors that increase the risk of developing dementia at a higher rate, including cardiovascular disease and increased inflammatory markers [23–25]. Inflammation in epilepsy is commonly attributed to the adverse effects of both seizures and antiepilepsy drugs (AEDs) [26]. In AD, inflammation is thought to contribute to disease progression and severity [27]. As such, the onset of seizures in patients with AD has been associated with a faster progression of disease symptomology and functional impairment [28, 29]. Specifically, epilepsy can result in a worsening of cognitive performance (particularly in language), a reduction in autonomy, a greater risk of injury, and a higher mortality rate among those with dementia [4, 28]. Volicer et al. (1995) found that 82% of dementia patients who suffered an initial seizure showed a sudden worsening of symptoms resulting in long-term care admission within 6 months of the seizure onset. However, such declines can be curbed with prompt, effective AED therapy and increased seizure control [30, 31].

Age is a clear risk factor for the development of both epilepsy and dementia. The incidence and prevalence of epilepsy increase with age throughout adulthood and are highest, approximately 25%, in patients over 65 years [13, 32, 33]. Considering that 5% of people over the age of 65 will develop dementia with incidence rates doubling approximately every 4–5 years [2], there is a very large population of people comorbidly affected by epilepsy and dementia. Comorbidity may be due to the fact that hippocampal sclerosis (i.e., severe neuronal cell loss and gliosis) is common in both disorders [34]. Structural and neurochemical brain changes resulting from chronic epilepsy may negatively impact cognitive function over time, making the brain of a

patient with epilepsy more susceptible to the development of dementia.

Shared Neurobiological Substrates of Seizures and Dementia

The neuropathological processes underlying both seizures and dementia are likely to play a role in the increased comorbidity rates of these disorders. However, the abnormal neurological mechanisms involved in each of these disorders are not fully understood. There is evidence to suggest that neuronal hyperexcitability, amyloid beta protein, and tau are contributing factors to the comorbidity of epilepsy and dementia.

Neuronal hyperexcitability is the primary process underlying seizure occurrence. In dementias, neuronal death that occurs in the context of degenerative disorders may offset the balance of inhibitory and excitatory neuronal functioning through selective loss of inhibitory neurons [35]. This imbalance ultimately leads to hyperexcitability and seizure occurrence. However, mouse models of AD have demonstrated both a decrease *and* an increase of neuronal activity. Interestingly, the increased neuronal activity, or "hyperactive" neurons, was found exclusively near beta-amyloid plaques [36, 37]. In fact, mouse models of AD revealed that high levels of amyloid beta protein are sufficient to elicit epileptiform activity even in early stages of AD and in the absence of overt neuronal loss [38]. Based on these models, there would appear to be an association between seizures and beta-amyloid plaques, a defining feature of dementia. In fact, amyloid beta protein was found to be elevated in surgically resected human temporal lobe tissue from patients with intractable epilepsy [39]. While amyloid beta appears to be a key factor in epilepsy and dementia, the cause for increased levels of amyloid beta remains unknown.

Increased levels of unstable tau protein are also characteristic of dementia and lead to the development of neurofibrillary tangles. Aggregates of tau are also found in patients with epilepsy and in experimental models of epilepsy [40]. Research has demonstrated that tau plays a role in the regulation of network synchronization, i.e., the balance of inhibitory and excitatory neurons. Mouse models have shown that when levels of tau are experimentally decreased, neuronal hyperactivity is decreased, which normalizes the balance between excitatory and inhibitory neuronal activity [41]. A normalization of this balance effectively increased the seizure threshold. However, in AD, where aggregations of tau are increased, a lowered seizure threshold would be expected. Consistent with this hypothesis, it is known that seizures are more common in patients with AD than in the general elderly population [16].

Although amyloid beta and tau appear to be likely contributors to susceptibility of seizures in those with AD, it is probable that there are multiple factors at play. In particular, comorbid vascular lesions, the apolipoprotein E (APOE) ε4 allele, and excessive neuronal cell loss in hippocampal and parietal cortices may also be factors involved in increased seizure occurrence in AD [8, 35, 42]. However, understanding the associations between amyloid beta, tau, and neuronal hyperexcitability lays the groundwork for the development of interventions aimed at these areas of the disease process and provides insight into the comorbidity of epilepsy and dementia.

Diagnostic Decision–Making in Patients with Seizures and Dementia

Epilepsy and dementia share common characteristics of cognitive decline and altered mental status which can mask the presence of the other disorder and lead to misdiagnoses; hence, the incidence of epilepsy in older patients may be two to three times higher than reported throughout the extant literature [5]. In particular, the absence of specific symptoms characteristic of seizures in younger adults may undermine an epilepsy diagnosis [5]. For at least half of all older adult patients who present with a symptom that ultimately was classified as a seizure, epilepsy was not initially considered as a primary differential diagnosis [5]. Rather, older adults with new-onset seizures often present with vague clinical symptoms, which increase the likelihood of misdiagnosis [43]. To illustrate, McBride, Shih, and Hirsch (2002) found that a dif-

ferential diagnosis of epilepsy was not considered in 73% of elderly patients who ultimately were diagnosed with epilepsy. Common initial misdiagnoses include altered mental status, confusion, "blackout spells," memory disturbance, syncope, dizziness, dementia, transient ischemic attack (TIA), depression, metabolic disorders, and/or psychiatric disorders [43–45]. As a result, patients treated with dementia drugs on initial diagnosis may show lack of symptom improvement due to untreated seizures [46]. In addition to the nonspecific presentation of seizure semiology in the elderly, a diagnosis of epilepsy is further complicated among older adults by potential coexisting cognitive impairment, which may lead to an incomplete history, under-reporting of events, a failure to recognize transitory confusional states, and absence of witnesses if patient lives alone [5, 47–49].

The vague clinical presentation of epilepsy in the elderly is quite different than what is typically observed in younger adults. For example, auras are less common and are often nonspecific (e.g., dizziness) and automatisms are less frequent [43]. Postictal states are frequently more prolonged in older adults, particularly if there is underlying brain dysfunction [50]. Postictal confusion may last as long as 1–2 weeks in an elderly patient, as opposed to minutes in younger individuals. This prolonged postictal confusion can be confused for dementia or delirium [5, 15, 47, 51]. Similarly, comorbid dementia can obscure the recognition of seizures. While the incidence of both focal and generalized epilepsy increases in older adults, the most dramatic increase is in focal epilepsy, and this is true of AD [16, 52]. In the elderly, focal onset seizures with alteration of consciousness are the most frequent seizure type [10, 53]. Secondary generalization of seizures is less common occurring in only 26% of elderly patients, as opposed to 65% of younger adults [45]. In older patients with chronic, rather than new-onset epilepsy, seizures may become briefer, and generalized tonic-clonic seizures may become less frequent or even disappear [54]. Additionally, while focal seizures most often arise from the temporal lobe in the general population, events of this type often originate from extratemporal or frontal regions in older patients, as these areas are often preferentially affected by stroke [5, 10, 52].

Status epilepticus (SE), a medical emergency associated with increased morbidity and mortality, is more common in older patients than younger adults. SE is a prolonged seizure lasting more than 30 min or a cluster of intermittent seizures lasting for more than 30 min, during which time the patient does not regain consciousness. In one hospital-based study, SE was the mode of presentation for first seizure in 25% of older individuals [55]. Stroke, either acute or remote, is the most frequent underlying etiology (in about one-third of patients) of convulsive SE [56]. The morbidity and mortality of SE are not only significantly greater in older adults [45], but rates increase with both seizure duration as well as number of comorbid medical conditions [57]. Mortality related to seizures can also occur through sudden unexpected death in epilepsy (SUDEP). SUDEP is an unexplained death of individuals with epilepsy, with no anatomical or toxicological cause found at postmortem examination. SUDEP is more common in younger adults, particularly those between the ages of 20 and 40 years, than in the elderly [58]. This is primarily due to the fact that older adults often have multiple comorbidities, in particular, cerebrovascular or cardiovascular disease. As such, distinguishing cause of death in an older adult with epilepsy as SUDEP versus cause of death related to a comorbid medical condition can be quite challenging, confounding estimates of the incidence of SUDEP in the aged population.

Common Differential Diagnoses

There are a number of diagnoses that can mimic seizures or dementia. It is of utmost importance to assess for the presence of these differential diagnoses to avoid unnecessary or inappropriate treatments and interventions, as well as to facilitate swift, aggressive treatment, when necessary. Medications for both epilepsy and dementia can have significant side effects, as well as drug-to-drug contraindications. Accurate diagnosis and treatment is particularly critical in older adults who are more susceptible to iatrogenic factors and to symptom exaggeration with inappropriate pharmacological interventions following a misdi-

Table 38.1 Common differential diagnoses

Disorder	Symptoms	Likely epilepsy if…	Likely dementia if…
Delirium	1. Disturbance in attention, awareness, and cognition 2. Develops over a couple hours to a few days 3. Fluctuates in severity over the course of the day	1. Relatively quick return to baseline cognition 2. Stereotyped motor movements or automatisms are present 3. EEG correlate	1. Cognitive symptoms with a gradual onset and progressive decline 2. Cognitive functioning does not recover
Transient ischemic attack	1. Typically begins with paresis 2. Typically non-stereotyped 3. Duration is approximately an hour	1. Paresis after event can occur 2. Isolated, complete, and brief speech arrest 3. Recurrent stereotypes events 4. Duration is typically less than 2 min 5. EEG correlate	1. Cognitive symptoms with a gradual onset and progressive decline 2. Cognitive functioning does not recover
Transient global amnesia	1. Striking, acute onset, amnesia 2. Usually last several hours 3. Patient can respond during episode	1. Acutely impaired cognition resolves relatively quickly 2. Lethargy following return to baseline cognition 3. Patient likely to be unresponsive or abnormally responsive during episode 4. EEG correlate	1. Cognitive symptoms with a gradual onset and progressive decline 2. Cognitive functioning does not recover
Syncope	1. Temporary partial or complete loss of consciousness with interruption of awareness followed by prompt return to baseline 2. Possible incontinence in elderly 3. No decline in cognitive functioning	1. Duration is typically less than 2 min 2. Lethargy following return to baseline cognition 3. Stereotyped motor movements or automatisms are present 4. EEG correlate	1. Loss of consciousness is uncommon 2. Cognitive symptoms with a gradual onset and progressive decline
REM sleep disorder	1. Vivid dreams that are acted out 2. No atonia	1. Vivid dreams are not acted out 2. Atonia during sleep 3. Stereotyped motor movements or automatisms are present 4. EEG correlate	1. Vivid dreams are not acted out 2. Atonia during sleep 3. Cognitive symptoms with a gradual onset and progressive decline
Psychogenic non-epileptic seizures (PNES)	Common features: 1. Likely history of traumatic event 2. Duration more than 2 min is common 3. Gradual onset 4. Fluctuating course of severity 5. Eyes closed 6. Side-to-side head movements	1. Duration typically less than 2 min 2. Stereotyped motor movements or automatisms are present 3. Incontinence (does not occur in PNES) 4. EEG correlate	1. Cognitive symptoms with a gradual onset and progressive decline 2. Cognitive functioning does not recover

agnosis. Table 38.1 shows common differential diagnoses for older adults with symptoms that may be associated with epilepsy or dementia. Getting a clear description of the event and history of symptoms, particularly from a reliable collateral source, is key to accurate diagnosis. Common differential diagnoses for seizures and dementia include delirium, transient ischemic

attack, transient global amnesia, syncope, REM sleep disorder, and psychogenic non-epileptic seizures (PNES). Below is a brief overview of these differential diagnoses. For a more detailed discussion of differential diagnoses common in the elderly with dementia or epilepsy, please refer to the following references [9, 59–63].

Delirium

Delirium may be difficult to distinguish from focal seizures with impairment of awareness, particularly in a patient with baseline neurologic impairment [64]. However, tremor, asterixis, and myoclonus are not uncommon in delirium. Hallucinations may be a feature of either condition. Duration of delirium is much longer than a seizure and can last up to a day. Severity of symptoms in delirium tend to fluctuate over the course of the event [3], whereas ictal and postictal cognitive changes show a steady improvement back to baseline.

Transient Ischemic Attacks (TIAs)

Transient ischemic attacks are commonly mistaken for seizures; however, they may also induce seizures. Brain ischemia produces reduced neural activity and produces symptoms, such as hemiparesis or hemisensory loss [60]. In contrast, seizures usually cause "positive" symptoms from neuronal hyperactivity. However, "limb-shaking TIAs" may represent a source of diagnostic confusion in this regard. The presence of limb shaking is a well-established sign of hemisphere hypoperfusion, due to severe carotid or middle cerebral artery disease [60]. Although a TIA is commonly considered as a cause for confusional episodes, confusion is rarely a manifestation of TIA, and chronic, recurrent stereotyped events are much more likely to be seizures than TIAs [60].

Transient Global Amnesia

Transient global amnesia (TGA) is a syndrome of abrupt and temporary (<24 h) disruption of anterograde memory. Features that distinguish TGA from seizures include: no clouding of consciousness, no focal neurological signs, full recovery of cognitive functions except for memories during the event itself, and rare recurrent episodes [65]. Among patients with TGA, repetition of the same statements or questions is commonly reported [65]. Compared to TGA, episodes of transient epileptic amnesia (TEA) are typically briefer (<1 h), commonly occur upon waking, have a high recurrence rate, and may be accompanied by other features suggestive of epilepsy such as automatisms or olfactory hallucinations [65].

Syncope

Syncope is characterized by a sudden loss of consciousness and muscular tone followed by spontaneous recovery of full cognitive functions. Classically, syncope occurs when the patient has been upright and is more likely when they are also hot and dehydrated [63]. Warning symptoms of syncope characteristically consist of feeling hot, sweaty, and lightheaded and experiencing visual changes (e.g., seeing stars, vision going white, black, grey, becoming blurred, closing in) and auditory symptoms (e.g., sounds seeming distant, muffled, distorted) [66]. Syncope is not associated with confusion or amnesia following the episode [67]. Syncope can be associated with orthostatic hypotension, hypoglycemia, and hyperglycemia.

Rapid Eye Movement Sleep Behavior Disorder

Rapid eye movement (REM) sleep behavior disorder is characterized by vivid dreams in REM sleep without the usual accompanying muscle atonia. This results in individuals "acting out" their dreams, especially when they are vivid or frightening [68]. Motor movements associated with the acted out dreams, such as kicking, running, and screaming, are common [69]. As such, these behaviors may resemble clinical features of

seizures. Patients are usually able to describe the dream, a feature that is helpful in distinguishing this from seizures [70]. REM sleep behavior disorder in older adults is most commonly associated with alpha-synuclein neurodegenerative disorders including dementia with Lewy bodies and Parkinson disease [69].

Psychogenic Non-epileptic Seizures

Psychogenic non-epileptic seizures (PNES) are episodes that resemble an epileptic seizure, but have no electrographic correlate. Psychiatric disorders, such as anxiety and depression, often underlie PNES. As such, assessment of emotional and behavioral distress, coping style, and personality factors play a key role in revealing the determinant of PNES. It is possible for PNES to have a late onset in older adulthood, and it appears to be about as common in the elderly as it is in younger adults [43, 71]. Although the clinical manifestations of PNES are fairly consistent across age groups, late-onset PNES episodes are distinct from those occurring in younger patients with respect to antecedent psychological trauma. In older patients, health-related traumatic events are more likely (e.g., falls, stroke, myocardial infarction), while in younger patients, antecedent sexual abuse is common [72].

Imaging and Mapping Diagnostic Tools for Seizures and Dementia

Diagnostic tests for epilepsy include both noninvasive and invasive diagnostic techniques. Noninvasive measures include EEG and brain imaging. Invasive measures can include subdural grid and strip electrodes, as well as intracranial depth electrodes. Both invasive and noninvasive measures are aimed at identifying seizure onset zone. For a discussion of these diagnostic techniques in the elderly with seizures, please refer to [73].

In 2012, the FDA approved the use of Amyvid PET scans as a diagnostic screening tool for AD. While increased specificity of this tool is likely to improve over time, Amyvid PET scans are currently best used to rule out a diagnosis of AD. The Amyvid PET scan utilizes a radioactive tracer with affinity for beta-amyloid. If an individual's beta-amyloid deposits on this scan are significantly higher than expected for same-aged, healthy, non-dementing individuals, that patient is considered to have an increased likelihood of dementia. Amyvid PET is a useful tool to clarify potential diagnoses, prevent inappropriate interventions, and guide treatment decisions [74].

Antiepileptic Drugs and Dementia

Appropriate selection of antiepileptic drugs (AEDs) for any epilepsy patient of any age is based on seizure type, patient characteristics, and side effects of the medication. However, older adults are at an increased risk to the vulnerability of side effects, toxicity of AEDs, and failing medications (i.e., poor adherence) due to adverse side effects [75]. Furthermore, higher rates of cognitive difficulties among the elderly increase risk of medication failure due to poor medication management (e.g., forgetting to take medications, taking the incorrect dose). Given these increased vulnerabilities, careful selection of AED treatment regimens that will have the highest success rate in older adults is critical to successful management of seizures. For example, slower, more gradual titration, monotherapy, and lower dosage are recommended for older adults [45, 76]. In fact, older adults are more likely than younger patients to become seizure free with low AED doses [45]. Additionally, the coexistence of comorbid medical, neurological, or psychiatric conditions is higher in older adults and may be a factor in choosing a particular AED considering side effects and interactions with other drugs. Combination therapy of AEDs with other medications may amplify adverse side effects common to both drugs [76, 77].

The most common side effects across all AEDs include sedation, slurred speech, unsteadiness, clumsiness, dizziness, nausea, and adverse cognitive and behavioral effects [78]. AEDs are typically classified as "old"

(developed before the late 1990s) or "new" (developed after the late 1990s). The new AEDs have better tolerability for all age groups and are likely to produce less adverse effects, particularly in elderly patients. This is important considering that older adults are often more susceptible to AED-induced cognitive side effects, ataxia, and dizziness, with a secondary increased tendency toward confusion and falls [73]. It is also worth noting that older adults are more susceptible to the sedative effects of benzodiazepines [79]. Therefore, AEDs such as clobazam should be avoided or managed carefully by experienced epileptologists. Detailed overview of AED risks and benefits in older adults are provided elsewhere [5, 10, 15]. While the extant literature on AED use in elderly patients is quite limited, the few available studies support the effectiveness and tolerability of lamotrigine (LTG) and gabapentin (GBP) in elderly patients [52]. As such, it is recommended that LTG and GBP be considered as initial therapy for older patients with newly diagnosed seizures [80].

Within younger adults, AED intervention is typically not implemented until a patient has experienced two or more unprovoked seizures. In older adults, it has been recommended that treatment be initiated after a single unprovoked seizure. Immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce recurrence risk within the first two years [81]. This is particularly true in the context of a prior stroke due to the high risk of subsequent seizures and their potential serious consequences, including falls or fractures [56, 82].

Surgical Interventions

In patients who have failed adequate trials of two tolerated and appropriate AED schedules, there is increased likelihood that their seizures are drug resistant. Regardless of timing of treatment initiation, seizures remain drug resistant in approximately 20% of elderly patients [83]. For younger adults with drug resistant, or intractable epilepsy, surgery is often a consideration. That said, offering surgical treatment to elderly patients is a controversial topic [84–86] due to concerns related to exacerbation of cognitive decline [85, 86]. However, there have been studies finding that cognitive outcomes following temporal lobectomy for epilepsy are similar across younger and older adults [85, 86], unless there is evidence of a presurgical memory impairment [87]. The decision to proceed with surgery in older adults should be considered on a case-by-case basis taking into account patient characteristics, support level, functional capabilities, and cognitive skill. The goal of surgery for any patient is reduced seizure burden and improvement in overall quality of life.

As alternatives to surgery, epilepsy treatments for drug-resistant seizures include vagal nerve stimulation (VNS) and responsive neurostimulation (RNS). VNS is a procedure in which a device is placed under the skin on the chest that sends electoral pulses to the brain via the vagus nerve. It is believed that these pulses disrupt the rhythmic pattern associated with seizures. There is limited research on VNS in the elderly; however, Sirven et al. (2000) showed that VNS in adults aged 50 years or older is well tolerated and efficacious.

RNS involves the placement of a device under the skull, which monitors brain wave activity. The device is attached to electrodes placed within the suspected seizure onset zone. When abnormal electrical activity is detected, the device signals an electrical pulse to the area of abnormal activity to stop seizure onset. There are currently no studies to date on RNS in the elderly. Research into the efficacy, tolerability, and safety of this procedure in older adults is warranted. Finally, laser interstitial thermal therapy (LITT) is a relatively new surgical intervention for drug-resistant epilepsy. This procedure uses heat to target and ablate tissue of suspected seizure onset zone. Research across all age groups receiving this intervention is needed to determine efficacy, tolerability, and safety.

Clinical Assessment

Neuropsychologists play a key role in the treatment of both epilepsy and dementia patients by quantitatively defining an individual's neurocognitive strengths and weaknesses and recommending appropriate interventions to improve overall quality of life. More specific functions of the neuropsychological evaluation within these populations include assessing cognitive and behavioral functioning to guide medication management, to assess the impact of seizures on cognition, to guide preoperative surgical planning, and to obtain a baseline of cognitive functioning by which to measure any changes in the future. Given the frequent fluctuations in symptomology across these disorders, particularly when occurring comorbidly, there are a number of considerations to be mindful of throughout the interview, assessment, and when making recommendations.

Clinical Interview

In addition to the standard information obtained during an interview, such as relevant background related to the presenting complaint, medical history, psychiatric history, developmental history, social history, and educational/occupational history, there are a number of additional considerations specific to dementia evaluations in individuals with seizures. Since there is a great deal of overlap between symptoms of dementia and epilepsy, careful history taking and evaluation of all areas of neurocognitive difficulties, behavioral changes, and mood symptoms are critical features of the examination in order to determine whether seizures are a potential etiology that deserve further neurological investigation [52]. A focus on a detailed understanding of onset and progression of symptoms and how these overlap with any changes in seizures, AEDs, other medications, medical comorbidities, and other relevant life events (e.g., retirement, death of a spouse) is key.

A current and accurate medical history is important in determining potential etiology of seizures. New seizure onset in older adults is commonly associated with cerebrovascular disease, stroke, metabolic disturbance, head trauma, infectious disease, tumor, and drug interactions, so it is important to get a clear medical history. Similarly, cognitive difficulties can be due to a number of etiologies, and particular attention should be paid to the presence of other medical conditions, symptoms of altered mental status, sleep problems, and psychological distress. In particular, depression and lower social support are common in older adults and can potentially negatively impact cognitive functioning [88, 89].

Obtaining collateral information is of utmost importance for older adults with epilepsy or dementia due to potential lack of insight into or awareness of cognitive difficulties as well as difficulty describing one's own seizures. It is also particularly important to assess level of independence with activities of daily living, since this is helpful in differential diagnosis and forming recommendations. Checklists or questionnaires assessing activities of daily living, such as the Bristol Activities of Daily Living Scale [90], may be particularly useful in this regard.

Test Selection and Assessment Process

Prior to selecting tests for use with older adults with epilepsy, careful consideration of the testing environment, ease of accessibility, and possible limitations is needed. Ideally, the testing environment should be a welcoming environment that may put an otherwise anxious patient at ease. This is particularly important with older adults, as they may have an increased sensitivity to the effects of cortisol (i.e., stress) on memory performance [91]. For example, if possible, the following are recommended: 1) conducting an initial interview separate from testing to allow the patient to acclimate to the environment prior to returning for testing, 2) having an evaluator sensitive to the needs of older individuals, 3) decreasing the emphasis on the memory component of tasks when providing instructions, and 4) conducting the assessment in the morning or the time

that reports suggest the patient is in their best mental state [92]. Accessibility of the testing environment may also ease anxiety in the elderly. Clearly navigated spaces for walkers and wheelchairs, as well as comfortable and sufficient chairs to accommodate accompanying family members can be helpful. Increased frequency of motor and sensory deficits (e.g., poor vision and hearing) in this population requires understanding any limitations of the patient and adapting tests appropriately.

Test selection should take into careful account the robustness of the norms available for older adults. The Mayo's Older Americans Normative Studies (MOANS) provide normative data for individuals between the ages of 56 and 95 [93, 94]. As in any neuropsychological evaluation, test selection should take into account the specific referral question. In the epilepsy population, measures to help localize and lateralize dysfunction should be included. The National Institute of Neurological Disorders and Stroke (NINDS) has put forth recommended tests to use for the assessment of patients with epilepsy. These measures were chosen by experts in the field of epilepsy for their validity within the epilepsy population. While these assessment recommendations are not an exhaustive list of potential measures appropriate for use with epilepsy patients, these "Common Data Elements" (CDE) were developed to increase the efficiency and effectiveness of clinical research and clinical treatment. Table 38.2 outlines the core suggested measures to use with an epilepsy population aged 16 years and above.

Given that these measures are not specific to older adults, additional consideration of measures appropriate for the use in an elderly population that may be presenting with symptoms of dementia is important. In particular, further attention should be paid to the domains of memory, language, and motor skills, which are areas commonly affected by primary neurodegenerative disorders. Furthermore, more global assessments are useful in assessing older adults who may not be capable of completing a lengthy neuropsychological evaluation. Elderly patients may become fatigued more quickly during testing, and a shorter battery is often necessary. In such situations, batteries such as the Dementia Rating Scale – Second Edition (DRS-2) [106] or the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [107] may prove particularly useful.

Table 38.2 NINDS common data elements for epilepsy

Domain	Recommended measures
Premorbid estimation	American National Adult Reading Test (AMNART) [95]
Intellectual functioning	Wechsler Adult Intelligence Test-Fourth Edition (WAIS-IV) [96], Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II) [97]
Learning and memory	Rey Auditory Verbal Learning Test (RAVLT) [98], Brief Visual Memory Test (BVMT) [99], Rey-Osterrieth Complex Figure [100], Wechsler Memory Scale: Visual Reproduction [101], Nonverbal Selective Reminding Test
Language	Boston Naming Test (BNT) [102], Controlled Oral Word Association Test (COWAT) [103], Animal Fluency
Visuospatial	WAIS-IV or WASI-II Block Design, WAIS-IV Perceptual Reasoning Index
Executive functioning	Trail Making Test [103], Digit Span subtest from the WAIS-IV, Wisconsin Card Sorting Test (64 card version) [104]
Processing and motor speed	WAIS-IV Coding and Symbol Search, Grooved Pegboard [105]

Depression is a common psychiatric comorbidity in individuals with seizure disorders; people living with epilepsy tend to report more depressive symptoms than individuals without seizure disorders [108]. In addition, older adults with epilepsy have been found to report higher levels of depressive symptoms when compared to both healthy age-matched older adults [109, 110] and older adults with mild cognitive impairment [111]. Depressive symptoms have been shown to negatively impact performance on neuropsychological tests in adults with temporal lobe epilepsy [112]. In particular, adults who exhibited depressed mood (as assessed by a semi-structured psychiatric interview) performed worse on measures of overall intelligence, visuoperceptual ability,

language, visual memory, and executive functioning, as compared to non-depressed adults with temporal lobe epilepsy [112]. Similarly, increased rate of depression in older adults with epilepsy (as measured by self-report questionnaires) is associated with diminished performance on measures of global cognitive functioning, memory, executive functioning, and verbal fluency, as compared to both healthy age-matched older adults [110] and older adults with milder impairments [111]. The use of mood measures specific to the aged population (e.g., Geriatric Depression Scale, Geriatric Anxiety Inventory) [113, 114] is recommended. Furthermore, given that poor insight is common among individuals with dementia, collateral report or clinician ratings of mood symptoms may be valuable. For example, the Hamilton Anxiety Rating Scale (HAM-A) [115] evaluates anxiety related symptomology evident during clinical interview.

Sleep problems may be of particular importance in older adults with epilepsy, as older age (i.e., 65 years and older) is associated with a shorter, lighter, and more disturbed sleep [116]. Perhaps more importantly, sleep problems in older non-demented adults are associated with diminished cognitive functioning [117, 118]. Specifically, Schmutte et al. (2007) reported that self-reported sleep complaints (i.e., delayed sleep onset and prolonged sleep duration) among older, community-dwelling, adults aged 75–85 were associated with significantly worse performance on measures of word knowledge, memory, visuospatial functioning, and fund of information. This relationship remained significant even after controlling for potential moderating factors such as: depression, sleep medications, age, education, and physical ailments. In contrast, only a small number of studies have investigated the role of sleep problems on cognition in elderly epilepsy populations; therefore, it is not yet possible to draw any conclusions on the impact of sleep on neuropsychological functioning in this group of individuals. However, given the known negative impacts of poor sleep on cognitive functioning, assessment of sleep in elderly individuals with epilepsy through instruments such as the Pittsburgh Sleep Quality Index (PSQI) [119] is recommended.

Assessment of Health-Related Quality of Life

The current research on health-related quality of life specific to older adults with epilepsy is extremely limited [120]. Despite the paucity of studies, elderly epilepsy populations are at increased risk for factors associated with diminished health-related quality of life, including depression [121], adverse side effects of AEDs [122], and comorbid medical illnesses [120]. The 31-item Quality of Life in Epilepsy (QOLIE-31) [123] is likely to be a useful tool in assessing health-related quality of life among elderly patients with epilepsy. This measure focuses more on the specific concerns of epilepsy patients and less on general health-related quality of life domains, such as pain and physical function. The QOLIE-31 is a self-report measure that consists of 31 questions assessing seven domains of seizure worry (7 items), overall QOL (2 items), emotional well-being (5 items), energy-fatigue (4 items), cognitive functioning (6 items), medication effects (3 items), social functioning (5 items), and an overall score.

Formulation of Findings

Consistent with standard practice in neuropsychology, outlining and describing the patient's cognitive profile in terms of their strengths and weaknesses is an important first step in conceptualizing neuropsychological functioning. Emotional, behavioral, and activities of daily living data should also be reviewed and integrated into the conceptualization of the case. If there is significant impairment, clearly describe the areas and severity of cognitive weakness. The profile of cognitive impairment should be contextualized in concert with relevant background information, medical history, psychological functioning, collateral information, behavioral observations, and imaging/lab tests.

All of this information should be reported within the context of the diagnoses being offered, if any. If possible, the extent to which these data are lateralizing or localizing should be discussed.

As noted above, AEDs carry risk for cognitive side effects. Determining the extent of AED impact on neuropsychological testing is an important consideration, particularly in the elderly who are at increased susceptibility to AED side effects. As such, noting cognitive complaints that coincide with changes in medications, dosage changes, and experiences of medication side effects should be documented in the report. Overlooking the possibility that medications are responsible for some cognitive inefficiencies potentially precludes the effective treatment of those symptoms by modifying the medication regimen [124].

Recommendations

Recommendations should always be tailored to the patient's particular strengths and weaknesses in the context of their individual needs. A list of common recommendations for patients with epilepsy and dementia is provided below for reference. Recommendations are divided into those addressing cognitive, medical, behavioral, and psychological issues.

Cognitive

- Interventions aimed at remediating deficits in particular areas of cognitive weakness need to be tailored to the patient's neuropsychological profile of strengths.
- Serial evaluation within 12 months, or sooner if clinically indicated, is often necessary to track changes in cognitive functioning over time; this is particularly important for patients with suspected dementia.
- Cognitive training or rehabilitation may be helpful within this population. Cognitive therapy often involves "brain games" that work to strengthen the connections in one's brain needed to complete tasks. Additionally, cognitive rehabilitation is helpful in developing compensatory strategies to "work around" areas of cognitive weakness.
- It is likely helpful to point to activities and lifestyle changes that can aid in cognitive improvement, such as 1) frequent and varied cognitively stimulating activities, such as reading, crossword puzzles, Sudoku, chess, etc., 2) moderate and regular exercise, 3) healthy eating habits, and 4) socialization.
- Individuals with poor functional independence in activities of daily living may benefit from more structure embedded into their daily lives and routine. For example, use of pill boxes, to-do lists, calendars, alarms, breaking things down into simple steps, and written copies of instructions are a few possible simple suggestions that may go a long way in increasing feelings of independence and self-efficacy.

Medical

- A recommendation to the patient's physician to review pharmacotherapy may be warranted if it is suspected that AEDs or other medications may be causing adverse cognitive or behavioral side effects.
- For both epilepsy patients and dementia patients, it is important to recommend that medications be closely monitored by their prescribing physician due to an increase risk of medication non-compliance in these populations.
- Medical decision-making abilities should be considered, such as assigning a healthcare proxy.
- Additional tests, including brain imaging and additional lab work, may be appropriate.
- If seizure activity is suspected, referral to an epileptologist for comprehensive evaluation is recommended.
- Given that cerebrovascular disease is a common etiology of both epilepsy and dementia, recommendations to reduce relevant vascular related risk factors that may be

impeding cognitive functioning are important.

Behavioral

- Safety interventions to address frequent difficulties with medication management, forgetting to turn off the stove, managing finances, and wandering or getting lost.
- Results of the neuropsychological evaluation may suggest that a formal driving evaluation is warranted.
- An assessment by an occupational therapist may be helpful to determine the patient's functional capabilities and whether or not modifications in activities are required.

Psychological

- Given the negative impact of anxiety/depression on cognitive functioning, it may be recommended that these concerns be addressed with formal psychotherapy or pharmacotherapy.
- Psychoeducation may be helpful to both the patient and caregivers regarding dementia and epilepsy in older age.
- Psychoeducation regarding effects of mood on cognition may be needed.
- Caregivers may experience high levels of stress, which, in turn, can impact care for the patient. Social support groups for caregivers are valuable to patient care.

In addition to the recommendations outlined, providing patients with resources to websites, support groups, help groups, and psychoeducation are important, tangible recommendations. Education regarding basic facts about epilepsy and its cognitive and mood implications can be empowering. There are several online resources for education and online forums for epilepsy in general as well as ones specific to seniors with epilepsy:

- Through the Epilepsy Foundation, patients can find information on seniors with epilepsy in their section, "Epilepsy and the Senior Community." More information can be found at http://www.epilepsy.com/learn/age-groups/epilepsy-and-senior-community.
- American Epilepsy Society: https://www.aesnet.org/for_patients.
- National Institute for Neurological Disorders and Stroke: https://www.ninds.nih.gov/Disorders/All-Disorders/Epilepsy-Information-Page.
- Center for Disease Control and Prevention: https://www.cdc.gov/epilepsy/index.html.
- Many states and cities have local epilepsy groups that can be helpful for locating services for the individual patient.

Case Report

Background An 81-year-old, right-handed, Caucasian woman with 12 years of education was referred for neuropsychological evaluation due to recent, new-onset seizures. Per family report, the patient experienced a recent fall and subsequently woke up on the floor without memory for prior events. She was hospitalized for 6 days with no further medical complications. Six months later, the patient experienced two episodes that were suspicious for seizures, which involved loss of consciousness and nausea. Three months later, the patient experienced an odd sensation on the top of her head and a feeling of profound exhaustion, followed by speech arrest and an alteration of consciousness. Subsequent to this event, she was taken via ambulance and experienced a generalized tonic-clonic seizure *en route* to the hospital. Brain MRI showed "prominent frontal and parietal convexity of subarachnoid spaces." Video EEG showed "left temporal slowing suggesting left temporal cerebral dysfunction."

From a cognitive perspective, the patient reported a diminution of abilities since these suspicious episodes, including increased forgetfulness, frequent episodes of anomia that included paraphasias, slowed thinking, and poorer balance and gait. That being said, she continued to manage her activities of daily living (ADLs) independently.

Table 38.3 Case study neuropsychological assessment results

ACS-TOPF	2011(%ile)	2013(%ile)	Direction of change
Total	86	79	–
DRS-2			
Attention	37	9	↓
Initiation/Perseveration	2	75	↑
Construction	16	9	–
Conceptualization	63	75	–
Memory	25	9	–
Total	9	37	↑
WASI-II			
FSIQ	25	21	–
Block Design	8	7	–
Vocabulary	62	63	–
Similarities	58	37	–
Matrix Reasoning	12	16	–
WAIS-IV			
Digit Span	37	63	–
Coding	75	84	–
Symbol Search	68	95	↑
CVLT-II/RAVLT			
Trial 1	7	3	–
Trial 5	7	<1	↓
Total Recall	16	<1	↓
List B	16	27	–
Immediate Recall	16	<1	↓
Delayed Recall	32	<1	↓
Recognition Hits	1	4	–
WMS-IV			
Logical Memory I	50	37	–
Logical Memory II	50	63	–
Grooved Pegboard			
Right (dominant)	<1	<1	–
Left	<1	<1	–
Trail Making Test			
Part A	27	7	–
Part B	<1	47	↑
Verbal Fluency			
FAS	75	87	–
Animals	–	13	NA
BNT			
Total + stimulus cue	–	55	NA
Stroop			
Word	25	–	NA
Color	3	–	NA
Color-Word	<1	–	NA
WCST			
Categories	–	47	NA
Total Errors	–	55	NA

(continued)

Table 38.3 (continued)

RCFT			
Copy	<1	–	NA
Immediate Recall	<1	–	NA
Delayed Recall	18	–	NA
BVMT-R			
Total Recall	–	<1	NA
Delayed Recall	–	<1	NA
Discrimination Index	–	3	NA
Mood			
BAI	7	14	↑
BDI-II	18	17	–

Note: *ACS* Advanced Clinical Solutions, *BAI* Beck Anxiety Inventory. *BDI-II* Beck Depression Inventory Second Edition, *BNT* Boston Naming Test, *BVMT-R* Brief Visuospatial Memory Test – Revised, *CVLT-II* California Verbal Learning Test Second Edition, *DRS-2* Dementia Rating Scale Second Edition, *FSIQ* Full Scale Intelligence Quotient, *RCFT* Rey-Osterrieth Complex Figure Test, *RAVLT* Rey Auditory Verbal Learning Test, *TOPF* Test of Premorbid Functioning, *WAIS-IV* Wechsler Adult Intelligence Scale Fourth Edition, *WASI-II* Wechsler Abbreviated Scale of Intelligence Second Edition, *WCST* Wisconsin Card Sorting Test, *WMS-IV* Wechsler Memory Scale Fourth Edition

In addition to presenting concerns, the patient's medical history was significant for hypothyroidism, hyperlipidemia, and peripheral neuropathy. Surgical history was significant for partial thyroidectomy, hip surgery following a car accident (no head injury), cataract repair, and gynecological surgery. At the time of the assessment, the patient was prescribed the following medications: lamotrigine, metoprolol, simvastatin, raloxidene, Caltrate, and levothyroxine. The patient's mother reportedly had an undiagnosed memory-related disorder. Family history was also significant for heart disease, stroke, and cancer.

The patient graduated from high school and held employment in clerical work. She was retired at the time of the assessment. The patient endorsed affective distress, including feelings of anxiety and fear, due to recent seizure episodes, and memory difficulties. Additionally, she reported that she often wakes up early and cannot fall back to sleep. As such, she often experienced fatigue throughout the day and has started taking a daily 1-h nap.

Clinical Assessment The patient was alert and oriented to person, place, and time throughout the assessment. Receptive and expressive language skills appeared intact during casual conversation, with no evidence of paraphasias. Her thought process was logical and goal oriented. However, the patient was observed to be distracted and talkative throughout the assessment, which often required redirection to the task at hand. Perseverative responding was also observed. Initial neuropsychological evaluation was conducted 10 months after first suspected seizure event, and a follow-up neuropsychological evaluation was administered two years later (Table 38.3).

For the purposes of this case presentation, a change in performance more than one standard deviation is indicated. It is worth noting that in clinical practice, reliable change indices (RCI) should be calculated to determine significant change in functioning over time [125]. From 2011 to 2013, the patient showed both improvements and declines in areas of cognitive functioning. Declines were observed in areas of memory and attention. Improvements were noted in areas of processing speed, aspects of executive functioning, oral motor skills on DRS-2, and manual motor skills on DRS-2. Although it is difficult to determine the factors involved in her cognitive improvement, it could be speculated that adequate seizure control is playing a role. The improvements observed in selected areas of functioning argue against the presence of a

neurodegenerative disorder. Furthermore, specific declines in verbal memory are consistent with seizure semiology of left temporal origin. Across both assessment points, variable attention was noted which impacted the patient's ability to learn new information. Finally, depressive symptoms remained consistent between the two assessments; however, anxiety levels reportedly increased. Even within the context of increased psychological distress, the patient was able to demonstrate improvement in performance. Given the patient's neurocognitive profile in 2013, as well as denied decline in activities of daily living, she would not meet the criteria for a primary neurodegenerative disorder. However, this is a patient that should be carefully monitored over time for a developing dementing process given her age and seizure disorder with associated cognitive changes.

Clinical Pearls

- It is important to clarify the referral issue before evaluation, as well as describe the purpose and structure of the evaluation.
- Always obtain collateral information when possible. Patients with both epilepsy and dementia may have difficulty reporting their own symptoms due to cognitive difficulties or limited insight.
- Level of independence in completing activities of daily living is important to assess for an accurate diagnosis of neurocognitive disorder (mild vs. major). Both basic and instrumental tasks of daily living should be assessed.
- In general, there is a high rate of medical and psychological comorbidity among individuals with epilepsy and dementia. It is important to obtain a comprehensive medical and psychiatric history and be aware of the effects of additional conditions on cognitive functioning.
- Common initial misdiagnoses include altered mental status, confusion, "blackout spells," memory disturbance, syncope, dizziness, dementia, transient ischemic attack (TIA), depression, metabolic disorders, and/or psychiatric disorders.
- Postictal confusion may last as long as 1–2 weeks in an elderly patient, as opposed to minutes in younger individuals. This prolonged postictal confusion can be confused for dementia or delirium
- Poor sleep is well known to negatively affect cognitive functioning, and poor sleep is a common comorbidity in both epilepsy and dementia. It is important to thoroughly assess sleep quality and sleep hygiene (e.g., how many hours do you sleep? Do you wake up during the night? Do you have trouble falling asleep/staying asleep? Do you feel rested in the morning? Is your sleep restful? Do you have vivid dreams/nightmares?)
- The assessment battery should be appropriate for both epilepsy and dementia patients with particular focus being paid to: keeping it short due to fatigue and a focus on language, memory, and motor skills.
- Assessing for depression and the impact of mood on neuropsychological results is key to deciphering diagnoses.
- It is important to use robust normative data available for older adults (such as the MOANS norms).
- Older adults often have a polypharmacy medication regimen. Understanding the cognitive impact of these drugs, alone and in combination with each other, is important when conceptualizing cognitive findings.
- Cognitive remediation therapy, individual or group, may help facilitate improvement of symptoms or reduce the rate of decline of cognitive functions.

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