

Epilepsy in Elderly

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Abstract

Advanced technology and life science significantly prolongs human's lifespan. The prolonged longevity enables people to enjoy longer life but adversely increases the mortality and morbidity of aging-related disorders which may, in turn, devalue the quality of late life. Of the aging-related neurological conditions, increased incidence and prevalence of convulsive disorders, namely seizures or epilepsies, have been documented in literature. Epilepsy is the third most common neurological condition after dementia and stroke among the elderly. Multiple risk factors cause the elderly to be prone to develop seizures or epilepsies, including advanced aging, stroke, traumatic brain injury, dementia, neurodegenerative diseases, brain tumors, obstructive sleep apnea, and obesity. In this article, we highlight the epidemiology, pathophysiology, and clinical manifestations of elderly seizures.

Keywords: Epilepsy; Seizure; Elderly; Senior; Risk factor

Introduction

Advanced civilization promotes longevity of human being. The term of senior, or elderly, is defined as a person over the age of 60-65 years and retired [1,2]. In 2010, 40 million people aged 65 and over accounted for 13 percent of the total population in the United States. The number and proportion of older Americans is expected to grow significantly to 72 million in 2030, representing nearly 20 percent of the population. The population aged 85 and over was 5.5 million in 2010 and will grow to 19 million by 2050 [3]. Although the prolonged lifespan enables people to enjoy longer lives, it also simultaneously generates many age-related health problems. Occurrence of convulsive disorders, namely seizures, is significantly increased in the elderly.

Seizure and Epilepsy

Seizure is a devastating but treatable medical condition caused by an abnormal paroxysmal time-limited hypersynchronous electrical discharges of the brain cortical neurons, manifesting as motor, sensory, and/or autonomic dysfunction with or without loss of consciousness. Epilepsy is a chronic disorder of the central nervous system (CNS) whose symptoms are recurrent seizures. Most new seizures in elderly patients are localization-related, termed as focal seizures with or without secondary generalization, such as simple or complex partial seizures, once commonly known as petit mal seizures. A simple partial seizure doesn't result in loss of consciousness but cause involuntary jerking movement of a body part, i.e. an arm or a leg; or sensory symptoms, such as tingling, dizziness and flashing lights. A complex partial seizure, previously termed temporal lobe or psychomotor seizure, results in alteration or loss of consciousness. Localization-related epilepsies are manifested with focal deficits resulting from specific functions of the respective brain areas. The location of neuropathology underlying epilepsy determines the

manifestation of seizures. For example, temporal lobe pathology can cause epilepsy with memory impairment; while pathology involving the language-dominant hemisphere may produce word finding and naming difficulties; and certain epilepsy syndromes are associated with severe cognitive or behavioral problems [4-6]. The generalized seizures in elderly, in contrast to 50% seen in children under the age of 15, are only seen in 25% of senior epileptic patients and usually occur following an anoxic insult [7-11]. They usually present as tonic-clonic convulsions, which were once commonly known as grand mal seizures. They may also evolve from localization-related seizures as the secondary generalization. Rarely, absence status epilepticus may occur in elderly, which can be caused by transient metabolic or toxic derangement such as benzodiazepine withdrawal, however, it usually does not need long-term antiepileptic medications [12].

A provoked seizure is an acute symptomatic episode that occurs in close temporal relation with the insult such as stroke, traumatic brain injury (TBI), or an otherwise obvious insulting metabolic or toxic attack which is presumed to be the underlying cause. In contrast, an unprovoked seizure occurs in the absence of one or any precipitating factors, and it includes events occurring in patients with antecedent stable (nonprogressing) (CNS) insults, or remote symptomatic seizures [13]. The definition of onset of an acute symptomatic seizure can be divided into two subtypes: early-provoked seizures as the events occurring within the first 7 days after a CNS insult, and late-provoked seizures as those occurring 7 days later. While an unprovoked seizure occurs in the absence of any precipitating factors, unprovoked epilepsy is the occurrence of repeated unprovoked seizures [14]. Status epilepticus is continuous seizures lasting 30 minutes or longer; or two or more discrete seizures between which there is incomplete recovery of consciousness [15,16].

Epidemiology

Epilepsy affects approximately 50 million people worldwide [17] including approximately 300,000 seniors in the United States. Epilepsy is frequently seen in the elderly [18]. 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 [10,19-21]. In individuals aged 65 years or older, dementia and other neurodegenerative diseases account for 9–17% of the causes for epilepsies [10,18,22-27]. By 75 years of age, 3% of the population will likely have epilepsy and 10% will have had a seizure of some type. In contrast, only 1% will have developed epilepsy by age 20 [28]. The annual incidence in population over the age of 60 years increased from 1.04 per 1,000 in people 65–69 years-old to 3.58 per 1,000 in those 85 years [7,27,29-34]. Epilepsy is the third most common neurological condition after dementia and stroke among the elderly [31].

Older adults are the fastest growing population group with epilepsy. Increase in prevalence of epilepsy among older adults may be due to multiple comorbidities that older adults frequently experience. For example, elderly are at an increased risk of stroke and heart attack, both of which can damage the brain and cause epilepsy. Indeed, stroke is the most common cause of seizures in elderly, causing about 33 percent of all cases of epilepsy. Elderly are also at risk for dementia, including Alzheimer's disease (AD), which is the second most common cause of epilepsy in seniors. In addition to their underlying medical conditions such as hypertension, atherosclerosis, and metabolic disorders with organ failures; traumatic brain injury (TBI) after a fall due to imbalance or weakness from peripheral neuropathy is also a significant risk factor. These medical conditions may damage the brain and result in seizures.

The most common etiologies for seizures in the elderly are cerebrovascular disease, toxic and metabolic encephalopathies, dementia, and brain tumors [23,24]. In patients with dementia, the incidence of seizures is 5–10 times greater than that in a reference population, and 10 to 22% of AD patients have at least one unprovoked seizure [35]. Patients with a combination of stroke and dementia were at a significant higher risk for development of epilepsy than patients with either a stroke or dementia alone [36].

The incidence of epilepsy increases with age after 60 years [37]. Almost 25% newly diagnosed epilepsies are over 60 years old. Epilepsy is a significant comorbidity in the elderly after stroke and dementia [38]. 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 [22]. 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 [23]. The estimated prevalence of epilepsy may be higher ranging from 13 to 50 per 1,000 depending on the population studied [22,39-41] and the estimated incidence ranges from 1.0 to 2.6 per 1,000 depending on age [10,42]. A recent study showed that prevalence of epilepsy in elderly is estimated 10.8 per 1,000 and the incidence of new-onset epilepsy is estimated 2.4 per 1,000 [43]. Prevalence and incidence rates were highest among African Americans, particularly African American men, which is consistent with earlier reports [44,45]. African Americans had almost twice the prevalence (18.7 per 1,000) and incidence (4.1 per 1,000) than Caucasians (10.2 prevalence, 2.3 incidence), while Asians (5.5 prevalence, 1.6 incidence) and Native Americans (7.7 prevalence, 1.1 incidence) had lower rates. Incidence rates were slightly higher for women than for men, and increased with age for all gender and race

groups. In contrast to the previous studies of higher prevalence and incidence in men [44,45], however, Faught and colleagues reported that men and women had similar prevalence and incidence [43].

Etiologies and Risk factors for Seizures in Elderly

Stroke

Stroke is an aging related disorder although it also affects youths. A recent report estimated approximately 795,000 Americans experience a stroke every year, which approximates to 1 stroke every 40 seconds [46]. In the United States, the most common cause of provoked seizures in elderly people is acute stroke [29,47-49]. Eight percent of patients will develop seizures within two weeks of a hemorrhagic stroke, compared with 5% among those who have had an ischemic stroke. Previous stroke occurrence is the most common underlying etiology, accounting for 30-40% of all cases of epilepsy. Asymptomatic cerebral infarction can also lead to epilepsy and, reciprocally, seizures may be a marker of increased risk for subsequent stroke [50]. The frequency of poststroke seizures varies from 2.3% to 4.5% [7,51,52]. In a long-term prospective controlled study of 484 patients with ischemic strokes, Lossius and colleagues reported that the prevalence of poststroke epilepsy was 3.1% in 7 to 8 years after an ischemic stroke. The occurrence has been shown to be related to the severity of stroke and worse Stroke Scale scores on admission, which is considered as a significant predictor for poststroke epilepsy [53,54]. In addition to the severity of a stroke, factors such as hemorrhagic stroke, cortical location of the stroke [53,55-60]; and late onset of the first seizure after a stroke [55,61-65]; have been found to predict poststroke epilepsy. Interestingly, age at stroke onset has not been found to predict poststroke epilepsy [66].

Seizures were more common in lobar hemorrhages but subcortical hemorrhages were found to be linked often with secondary generalization [67]. Occurrence of posthemorrhagic seizures was associated with neurologic worsening on the NIH Stroke Scale and with an increase in midline shift. In a prospective study on patients with ischemic stroke (n=46) and intraparenchymal hemorrhage (ICH) (n=63) with continuous electroencephalograph (EEG) monitoring for 72 hours after admission, Vespa and colleagues observed that electrographic seizures occurred in 28% ICH patients, compared with 6% ischemic stroke (OR=5.7, 95% CI: 1.4 to 26.5, $p < 0.004$) and there was a trend toward increased poor outcome [67]. It is evidenced that stroke is the most common risk factor for seizures in the elderly population accounting for 39–45% of all seizures [68-70]. 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) [32].

Traumatic brain injury

Elderly are at increased risk for TBI, which is an important factor to cause seizure and epilepsy because of elderly's pathophysiologic conditions and prone to falls. Post-traumatic epilepsy (PTE) is a recurrent seizure disorder following a head trauma. It can occur immediately or years after the brain injury. In a recent population-based study of 2,118 patients hospitalized with TBI, 115 (5.4%) developed epilepsy in 2–3 years following hospital discharge [71]. A previous study indicated that up to 20% elderly epilepsy can be caused by TBI [72]. PTE accounts for approximately 20% of symptomatic epilepsy in the general population and 5% of all epilepsy patients [73-76].

Increased TBI severity increases risk of late posttraumatic seizures (PTS) or PTE [73,77-79]. Notably, early PTS may be a risk factor for late seizures or epilepsy in adults [77,80,81]. Findings of 26% of hospitalized TBI cases with early PTS progressing to unprovoked seizures in a 10-year retrospective study suggested that seizures are an important neurologic complication of TBI [82]. A prospective study of hospitalized adults with TBI in Europe showed early PTS is the strongest risk factor for PTE [83]. Interestingly, there was no difference in risk of PTE by gender [71,83] and race [71] but higher prevalence of epilepsy among individuals aged 45–64 years and those with lower education and income as shown in a population-based study [84]. Seizures following TBI have been reported as more common in elderly [73]. The reported overall incidence of late PTS or PTE has a range of 13–50%, depending on the population studied and the follow-up time, with the highest incidence coming from studies of war veterans, among whom penetrating TBI is more common than among civilians [77,78,80,81,83,85-87].

The precise mechanism by which a trauma to the brain tissue leads to recurrent seizures remains unknown but the resultant cortical dysfunction plays an important role in the genesis of the epileptic activity. Pathogenesis of causing early seizures likely differs from that of causing late seizures [88-90]. Subdural hematoma is a potentially treatable cause of epilepsy in elderly people. Interestingly, clinical observation suggests that the treatment of early PTS does not influence the incidence of late PTS or PTE, therefore, routine prophylactic administration of anticonvulsants is not recommended for patients with head injuries, and treatment in the acute phase does not reduce death or disability rates [91-99]. However, according to the latest guidelines issued by the Brain Trauma Foundation, the American Academy of Neurological Surgeons (AANS), and Congress of Neurological Surgeons (CNS) for the management of severe TBI, seizure prophylaxis is recommended during the first seven days after TBI (level II) [100].

Dementia and neurodegenerative diseases

Age is a common risk factor for both epilepsy and dementia. The prevalence of dementia is estimated approximately 6–8% after 65 years of age and may rise to 20–30% in individuals older than 85 years [101-103]. Strong evidence from ample clinical studies has been shown that seizures are more frequently seen in Alzheimer's disease (AD) patients than in the general population [25,104-107]. AD is a progressive neurodegenerative disorder and is the most common cause of dementia among older people. Patients with AD are up to ten times more likely to develop epilepsy than those without AD [25,108] and seizures usually develop in the advanced stage [70]. Advanced AD alone is an important risk factor for late-onset seizures [105,107,109,110]. Epilepsy in dementia has significant consequences on the prognosis of the underlying dementia. Seizures worsen cognitive performance, particularly in language, and compromise autonomy leading to an increased risk for injury and mortality rate [111-113]. Language functions declined more rapidly in AD patients with seizures than in those without seizures matched by age and duration of AD [111-113]. Additionally, these patients are vulnerable to the adverse effects of medications and their conditions may suddenly worsen and require an admission to a long-term care facility within 6 months of the seizure onset [113-116].

Although AD is the most common form of dementia, other causes include vascular disease, Lewy body disease, and frontotemporal lobe dementia [117]. Dementia has been estimated to account for 10–20%

of all epilepsies in elderly [118]. Ironically, younger age is a risk factor for seizures in dementias [106,107]. The overall incidence of unprovoked seizures in AD is higher than in age-matched general population (hazard ratio, 8.06; 95% confidence interval, 3.23-16.61). A proportion of 2 to 13% of AD patients would have a seizure within 5 years of dementia diagnosis [107]. AD and other dementias are associated with a 5-10 fold increase in risk of epilepsy when compared with the control population [119,120] and, by the tenth year after diagnosis, 15% diagnosed AD patients will develop epilepsy [25,119]. Amatniek et al. [106] evaluated the cumulative incidence of AD/seizures and identified comorbid medical and psychiatric baseline conditions that could influence the risk of an unprovoked seizure in patients with mild AD. They found the cumulative incidence of unprovoked seizures at 7 years was almost 8%. Independent predictors of unprovoked seizures are younger age, African-American ethnic background with severe dementia and focal epileptiform activity on EEG. Additionally, seizures are more likely to occur with early-onset disease, particularly in the familial form with presenilin-1 mutation [121-124]. However, controversies exist. No association between seizures and patient age at the onset of AD nor between seizures and any prior EEG findings were also noted [105]. Compared to AD patients without seizures, AD patients who had seizures were not different in other medical conditions, the medications they took, or the degree of focal pathology [105,125].

Generalized tonic-clonic seizures are common in AD patients which have presumably been evolved secondarily from a partial seizure focus [108,125,126]. Complex partial status epilepticus [111] and myoclonus [126] have infrequently been encountered. EEG is a useful tool aiding in the diagnosis. In a VA cooperative study including EEGs, which enrolls patients who are 60 years and older with new-onset epilepsy and excludes patients with progressive neurologic conditions (including dementia and primary brain tumors), epileptiform activity was present in 37% of routine EEG [127]. In a study of 254 patients with AD, Smits and colleagues reported significant EEG abnormalities were associated with different cognitive profiles in AD. Only 28% of these patients had a normal EEG, while 32% had focal abnormalities, 14% diffuse abnormalities and 26% had both focal and diffuse abnormalities [128]. Seizure incidence is increased in people starting with mild-to-moderate AD. Younger individuals, African Americans, and those with severe dementia or focal epileptiform findings on EEG were more likely to have unprovoked seizures [106]. However, Liedorp and colleagues reported epileptiform discharges were seen in only 3% (42 of 1,674) patients with AD and other forms of dementia on routine EEGs, suggesting the rate was very similar to those of the general population [129]. The discrepancy in EEG findings may be due to multifactors, including variations in EEG acquisition, such as length of recording, appropriate montage; use of medications among the other factors [130-134] and even the oily scalp may affect the recording. In fact, a focal slow, such as delta, activity can be considered relevant to be epileptic in elderly due to a focal deep white matter pathology, however, temporal slow-wave activity may be a normal consequence of aging [135,136].

The nature of the underlying mechanism for unprovoked seizures in AD remains unclear. Hippocampal neuronal degeneration is the most common abnormal lesion identified in temporal lobe epilepsy and it has been reported in many different dementias, including AD, dementia with Lewy bodies or fronto-temporal dementia [137]. Mutations in the α -synuclein gene that are associated with hereditary Parkinson's disease and Pick's dementia have also been shown to have

an increased risk for the development of progressive myoclonic epilepsy with generalized tonic-clonic seizures [138]. Longitudinal clinical follow-up in patients with EEG, SPECT and CSF biomarkers suggested an underlying encephalopathy with cortical involvement [139]. The role of a disproportionate neuronal degeneration in the parietal and hippocampal areas has been postulated to be the neuropathological substrate of seizures in AD [110]. A relationship between cell loss in the CA1 area of the hippocampus with a high density of A β plaques and neurofibrillary tangles, and the occurrence of seizures has been postulated in patients with familial AD. In mouse AD models, constituents of amyloid- β (A β) plaques deposited in hippocampal circuits have been demonstrated to be epileptogenic [140,141]. The role of the accumulation of A β plaques, neurofibrillary tangles and extensive neuronal cell loss in limbic and association cortices has been suspected [35]. The accumulation of A β -plaques may also play a role in epileptogenesis for seizures as in the cases of A β -related angiitis [142]. Animal studies have demonstrated that introduction of high levels of A β is sufficient to elicit epileptiform activity in vivo in the absence of frank neurodegeneration [143,144], which suggests that the primary effect of A β in provoking a seizure is due to aberrant network synchronization, rather than a secondary consequence of extensive neurodegeneration [140,143]. Additionally, neuronal loss in AD may consequently affect GABAergic inhibitory circuits and the balance between excitation and inhibition which may induce seizures [125]. An alternative to the role of histopathological lesions could be the selective loss of inhibitory neurons which may facilitate the occurrence of seizures [125]. The aberrant excitatory neuronal activity represents a primary upstream mechanism that may contribute to the epileptogenesis in AD [140].

Brain tumors

Brain tumors are a recognized risk factor for epilepsy in elderly people [70]. More than 17,000 people in the United States are diagnosed each year with a brain tumor. An estimated 10% to 20% of seizures are associated with tumors while brain tumors have been found in 32.9% of the elderly patients [7,22,27,145-147]. Seizures might be the first symptom of, and particularly common with, slow-growing tumors. Approximately 30% to 50% of brain tumor patients may have a seizure by the time their tumors are diagnosed, and an additional 6% to 45% of patients who do not initially present with seizures would eventually develop them [148-150]. Characteristics of brain tumors and their mechanisms in causing seizures in patients are incompletely understood [149,151].

Frequently associated with seizures are low grade well-differentiated gliomas [151-155], cortically located tumors [148,156-159], particular location in the temporal or frontal and motor or sensory cortices [151,160,161]. The most common types of brain tumors that are found to produce seizures in later life are gliomas, meningiomas and metastases [147], especially located in the convexity of the brain. Meningioma is known to be one with a higher incidence of epilepsy [162,163]. Notably, rapidly growing tumors, such as high-grade gliomas, particularly those situated in deeper structures, usually present with non-seizure-related symptoms. Patients with high-grade tumors in the pericallosal region, such as glioblastoma multiforme, were significantly less likely to present with seizures, even the high-grade tumors in the temporal lobe [164]. While low-grade gliomas, such as those located in the temporal lobe or the insula grow large without other symptoms and eventually cause seizures [164]. Patients with low-grade tumors were more likely to present with seizures if their tumors were situated in the temporal lobe or in the insular

cortex. In other words, rapidly growing tumors cause symptoms related to mass effect, such as headache, cognitive deficits, or focal weakness, rather than seizures; while the low-grade tumors, or large tumors were more likely to present with seizures than small tumors. Importantly, tumors located in the insular cortex are likely to be clinically silent until the patient experiences a seizure. A retrospective study showed 50 out of 51 insular grade II gliomas patients presented with seizures and 45 of them had a normal neurological examination [165]. Insular cortex is often a region of seizure spread in temporal lobe epilepsy. Clinically, seizures originating from the insular region are difficult to distinguish from those arising from temporal lobe [166] and 10% of patients initially thought to have temporal lobe epilepsy may in fact have seizures originating in the insular cortex [167]. High frequency of preoperative seizures has been reported in other smaller series describing low-grade insular tumors [148,168-171]. Interestingly, if a seizure occurs, high-grade tumors presenting with seizures are likely to be smaller than those presenting with other symptoms [164]. Notably, the left hemisphere tumors are less likely to present with seizures, perhaps because of increased presentation with other neurological findings as a result of greater eloquence of the dominant hemisphere [164]. Advanced imaging techniques allow early detection of the lesions and characterization of their propensities to cause seizures at presentation [172,173].

Prophylactic anticonvulsant therapy has been proven to be ineffective in preventing seizures in patients with brain tumors in multiple large-scale studies [158,174-176], and it is not recommended by the American Academy of Neurology [150]. Nonetheless, prophylaxis remains a widespread practice because of difficulty in determining which patients are at greatest risk for seizures.

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repeated episodes of complete or partially blockage of the upper airway during sleep. OSA is widely underdiagnosed [177] and is associated with significant morbidity and mortality due to intermittent anatomical blockage of the upper airway and consequential reduction or cessation of airflow. OSA is associated with many medical conditions including neurocognitive dysfunction [178], irritability, lack of energy and depression. Untreated OSA worsens seizure control [179] and is associated with a variety of potentially life-threatening conditions including cardiac arrhythmias, hypertension, stroke, and myocardial infarction. OSA affects up to 24% of men and 9% of women [180] and is even more common in epilepsy, affecting more than 30% of patients with intractable seizures [181]. OSA has been documented in obesity and increases in incidence and prevalence with aging [181-186], males [181,182,184,187], hypertension [186,188,189], and type 2 diabetes mellitus [190-194] with Epworth Sleepiness Scale (ESS) score of 10 or greater [195] and sleepers [181,184]. Individuals with OSA may rarely be aware of having difficulty breathing, even upon awakening but may have daytime sleepiness, insomnia, morning headaches, fatigue, forgetfulness, difficulty concentrating, mood changes such as irritability, anxiety, and depression. Common symptoms suggestive of OSA include snoring, restless sleep, daytime fatigue and sleepiness [196]. Common signs of OSA include unexplained daytime sleepiness, restless sleep, and loud snoring. Less common symptoms are palpitation, increase in hypertension, decreased sex drive, unexplained weight gain, increased nocturia; gastroesophageal reflux disease; and heavy night sweats. The hypoxia caused by OSA may cause structural and functional alteration

of neurons in the central nervous system (CNS). Neuro-imaging revealed evidence of hippocampal atrophy in OSA.

On the other hand, epilepsy worsens OSA. Studies have shown that patients with epilepsy are at higher risk for apnea than the general population (10.2% vs. 4%) [184], due to sedentary lifestyle or the adverse effects of antiepileptic drugs (AED) [181]. Clinical studies showed that 30% women and 73% men, who had epilepsy and aged 50 years and older, had an AHI of 5 or greater, suggesting OSA and epilepsy in older adults are comorbidities [179,183], particularly in obese individuals [197]. This comorbidity represents a diagnostic challenge because OSA can mimic seizures during sleep [198-200].

Sleep fragmentation in OSA can facilitate the occurrence of seizures and increase drowsiness in epilepsy patients [201], whereas epileptic seizures can induce apneas [202]. The coexistence of epilepsy and OSA may reciprocally aggravate the clinical course of each condition. Primarily, incidence of both OSA and epilepsy increases with age. The presence of OSA has been found higher in patients with refractory epilepsy [181,184,203-207] but lower in general populations [184,205,208-210]. Patients with epilepsy have been shown to be more likely to have OSA because of nocturnal seizures, use of CNS suppressing medications, and sedentary lifestyle. The appearance of OSA symptoms coincided with a clear increase in seizure frequency or the first appearance of status epilepticus [211]. OSA leads to increased disturbances of cardiac, respiratory, and metabolic conditions, including hypertension, stroke and congestive heart failure, all are potential risks for seizures [212]. Older adults with new onset seizures or worsening epilepsy were more likely to have OSA than similarly-aged patients without OSA [179]. Multiple case series have shown its coexistence with epilepsy [179,184,201,204,213-215]. Treatment of OSA reduces seizure frequency and improves seizure control in medically refractory cases [196,201,204,209,213,214,216,217]. Finally, epilepsy surgery candidates who had OSA were more likely to have nocturnal seizures than those without OSA [181] and OSA surgery reduces seizure frequencies in children [218].

Several mechanisms may contribute to the increased incidence of OSA in patients with epilepsy. The adverse effects of AEDs on CNS; decrease in arousal threshold and upper airway muscle tone, weight gain; and reduced physical activity of patients with epilepsy; all can adversely affect OSA [219,220]. Barbiturates and benzodiazepines may precipitate or exacerbate OSA [221,222]. Weight gain, which is most notably seen with valproic acid and carbamazepine in both children [223] and adults [222,224], may lead to clinically significant OSA in predisposed individuals. A prospectively randomized clinical trial in nearly 700 adults when adjusting for gender, age and smoking habits demonstrated that weight changes proportionately correlated with the changes of AHI over time [225]. At the lower range of AHI, each 1% change in weight was associated with a 3% difference in AHI, therefore, an increase in body weight of 10% resulted in an increase in AHI of 30%. Individuals with epilepsy are usually less physically active than age-matched controls as demonstrated by significant differences in aerobic endurance, muscle strength endurance and flexibility, and greater body mass index (BMI) [226,227].

It is well known that sleep deprivation can activate epileptic activity as depicted during EEG or occasionally cause seizures in subjects without pre-existing epilepsy [228-234]. Notably, sleep deprivation facilitates interictal epileptiform discharges independent of the activating effects of sleep [235]. Sleep deprived mice become hyposensitive to diazepam, which may be due to alterations in the function of the GABA receptor [236]. Ironically, sleep deprivation has

not been shown to increase seizure frequency during inpatient video-EEG monitoring [237], although questionnaire studies have shown a relationship between relative sleep deprivation and seizure frequency in temporal lobe epilepsy [238]. Polysomnogram (PSG) did not differ significantly between patients with or without OSA. But AHI in REM positively correlates to latency to slow wave sleep and the number of awaking showing that patients with epilepsy and OSA have significantly longer sleep latency and higher arousal index [239]. OSA tends to be worse in REM sleep whereas REM sleep induces skeletal muscle atonia, making the upper airways more susceptible to collapse [239].

Treatment of OSA improves seizure control in medically refractory cases [217] and reduces seizure frequency and severity in both adults [179,196,201,206,208,209,213,216,217,240-244] and children [209], possibly by consolidating sleep and reversing the effects of sleep deprivation. The effects of treatment of OSA in the patients with coexistence of OSA with epilepsy have been evidenced [201,204,209,213,216,241,245]. CPAP therapy may particularly benefit those OSA patients with generalized epilepsy, because of the influence of sleep and arousal on thalamocortical networks [246], and those with seizures that occur predominantly or exclusively during sleep, because of the influence of sleep stage transitions in facilitating seizures [181]. CPAP treatment in adult epilepsy significantly reduces the frequency of interictal spikes on EEG-PSG studies [247] and the improvement in seizure control particularly in obese patients [248]. Treating OSA may also allow for better tolerability of AEDs in patients with daytime sleepiness which is a major adverse effect of AEDs [245]. Improvement in seizure control, daytime sleepiness, or both has been demonstrated when OSA is effectively treated. Notably, a case report claimed OSA surgery was able to reduce seizure frequency in children [218]. Interestingly, moderate severity of OSA had been improved after a successful resection of left premotor frontal lobe in a young man with intractable focal epilepsy [249]. Improvement of epileptic seizures has been documented in effective treatment of OSA [201,206,208,213,216,217,241] by showing a reduction of interictal spikes on EEG [247] and 40-57% of patients with improvement in seizure frequencies independent of their AED changes. Epilepsy patients with OSA who used CPAP and were compliant with its use over a minimum period of 6 months had a better seizure control than those who were noncompliant with its use. Non-CPAP compliant patients had a >1.5-fold increased risk for ongoing seizures as compared to CPAP-compliant patients, suggesting that treatment of OSA may contribute to better seizure control and seizure freedom in patients with epilepsy [241]. Vendrame and colleagues showed 57% (16/28) of CPAP compliant patients became seizure free compared to 10% (3/28) of noncompliant patients in a retrospective study [241]. Uncontrolled series and randomized pilot trials demonstrated the benefits of CPAP on seizure frequency in adults [196,201,209,213]. Interestingly, all the refractory epilepsy patients with OSA who were compliant with CPAP showed significant improvement in their seizure control [217], however, Malow and colleagues showed there was no significant difference in seizure reduction in severely refractory epilepsy patients after CPAP treatment compared with the sham CPAP group [196], suggesting that the hypoxic effects in severely refractory epilepsy population might have been too advanced to be reversed by CPAP therapy. Nonetheless, early and appropriate treatment of OSA may improve symptoms and quality of life in patients with epilepsy.

Obesity

Obesity is a chronic medical condition. In the United States, over two-thirds of adults are overweight, and one-third of the adult population suffers from obesity [250]. There is a higher prevalence in certain ethnic populations, including African-, Asian-, and Mexican-Americans [251,252]. There are two most common measures in classifying obesity: BMI and waist-to-hip ratio. BMI is a ratio of body weight in kilograms divided by height in meters squared which is widely used for estimating body fat for most adults between 19 to 70 years of age, and correlates well with total body fat content in adults. An adult who has a BMI of 25-29.9 is considered overweight and over 30 obese. BMI of 35-40 is classified as severe obesity, 40-44.9 morbid obesity, and BMI greater than 45 is super obesity [251,253]. The waist-to-hip ratio (in inches) is obtained by measuring the waist at its narrowest point and the hips at the widest point, in order to estimate where the fat is deposited. The pattern of body fat distribution differs in men and women. Women usually deposit fat in their hips and buttocks, displaying a "pear" shape, while men deposit fat in abdomen, making an "apple" appearance. Waist-to-hip ratios of greater than 0.8 in women and more than 1.0 in men are "apples". Apple-shaped individuals are more likely to suffer from medical problems related to obesity [253]. Obese patients, especially those with a central distribution of fat, or "apples", have an increased risk of various medical disorders such as cardiovascular disease, stroke, and diabetes [251,253].

Obesity may be linked with a plethora of medical conditions such as degenerative osteoarthritis, diabetes mellitus, hypertension, cardiac disease, OSA, depression, dementia, stroke, headache, neuropathies, multiple sclerosis, and certain types of cancer [253]. In epilepsy, body weight gain is a common adverse effect from some AEDs, particularly valproic acid and carbamazepine, however, whether there is correlation between the obesity and increased risk of seizures in seniors remains to be elucidated.

Seizure mimics in elderly

Several types of transient episodes mimic seizures. Syncope can be confused with a seizure because of the presentation of a sudden fall with transient loss of consciousness and muscle twitches or myoclonus, tongue biting and urinary incontinence. The etiologies for syncopies are mainly cardiovascular. Transient global amnesia (TGA) can also be confused with a seizure event, particularly epileptic amnesic syndrome (EAS) or transient epileptic amnesia (TEA) [254], which is a type of temporal lobe epilepsies [255,256]. TGA is a well-described syndrome for more than 50 years with a characteristic of a temporary but almost complete inability to retrieve short-term memory with a range of problems accessing older memories. A person in a state of TGA exhibits no other signs of impaired cognitive functioning but recalls only the last few moments of consciousness, such as his or her own name [257,258]. TGA is usually seen in a middle aged or older person presented with an abrupt onset of severe anterograde amnesia, usually accompanied by repetitive questioning. During the attack the patients remained alert and communicative, no clouding of consciousness or loss of personal identity, absence of neurological signs or deficits, no features suggesting epilepsy or active epilepsy, no recent head injury, and resolution within 24 hours [258-264]. TGA is sometimes difficult to differentiate from EAS or TEA. Like TGA, EAS or TEA usually occurs in the elderly in good health without any history of cognitive disturbances. It consists of repetitive and transient memory impairment, which lasts a few

minutes. It may be the sole manifestation of a seizure or following a seizure. Amnesia in EAS or TEA is anterograde, retrograde or both and is sometimes associated with a few behavioral abnormalities (e.g. perplexity), with no memory of the episodes [254]. EEG may be normal or show nonspecific or paroxysmal abnormalities prevalent in the temporal regions especially recorded during sleep or after sleep deprivation. Brain CT or MRI scans are normal or show nonspecific moderate atrophy, generally prevalent in cortical and particularly temporal regions [254]. The duration, usually 4-6 hours in TGA but usually less than 1 hour in EAS or TEA; the number of attacks, repetitive episodes in EAS or TEA may help to distinguish TGA from EAS or TEA. It was argued whether TGA is clinically reminiscent of transient epileptic amnesia, which may have an epileptic or ischemic origin. Independent mesial temporal lobe spike discharges also have been described in TGA which may be due to transient ischemic attack [265-272]. Amnesia in epileptic patients has usually been considered an ictal or postictal manifestation [273]. EAS or TEA is a treatable unrecognized cause of episodic amnesic wandering and disorientation, which can be seen in AD and demented patients with epileptiform activity [140,274]. Empiric treatment with AEDs reduces episodic behavioral changes of transient amnesic wandering spells caused by ictal or postictal epileptic events [254,255,269,274,275].

Many patients with AD experience fluctuations in cognitive functions such as transient episodes of amnesic wandering and disorientation [144,276]. Epilepsy itself has a significantly adverse impact on the quality of life in patients with seizures. Seizures can worsen cognitive performance, particularly in language, decrease autonomy, and increase risk of injury and mortality rate. In elderly with dementia, seizure activities, particularly complex partial seizures, may be manifested as a decline in cognitive functions and worsening in the performance of activities of daily living with episodes of confusion [274]. It can be mistakenly considered as a symptom of the underlying dementia. Old adults with epilepsy can also present with non-specific symptoms like dizziness, altered mental status, or unresponsiveness, however, there are no reliable markers, particularly in elderly seizures with neurodegenerative disorders [277]. The intermittent inability to retrieve memories cannot be easily explained by relatively protracted processes such as neuronal loss, plaque deposition, or tangle formation. It seems more likely due to abnormal neuronal network activity. Epileptiform EEG discharges such as spikes and sharp waves have been documented in AD patients with amnesic episodes [274] and these specific cognitive disturbances and the associated epileptiform EEG discharges can be eradicated by administration of AEDs [274]. On the other hand, epileptiform discharges in temporal lobe epilepsy patients may cause memory disturbances simulating AD-like clinical phenotype [278].

Treatment of seizures in elderly

Management of seizures in seniors must be individualized because of the varieties of their seizure types and comorbidities [279,280]. The pathophysiologic conditions in seniors are generally compromised when compared to young adults.

Although treatment for epilepsy may stop seizures or decrease the severity and frequencies of epilepsy and have beneficial effects on cognitive performance, adverse effects of AEDs can cause untoward cognitive and behavioral effects [281-283]. Indeed, AEDs are a common cause of such morbidity [284,285]. Epilepsy surgical intervention may partially reverse or prevent cognitive deterioration, but left-temporal resections have a high risk of postoperative verbal

memory impairment [286], however, cognitive disturbance after epilepsy surgery in most cases can be minimized or avoided [287,288].

Conclusion

Epilepsy is a frequently seen and significantly increased in elderly. The diagnosis of a seizure is a clinical challenge, particularly in demented patients since they often remember little of the episodes. The diagnosis of a seizure is essentially a clinical exercise based on a reliable history, most often based on questions to the caregiver. Corroborative evidence from the caregiver or an observer is important. The most common cause of provoked seizures in elderly is acute stroke. Elderly are at increased risk for TBI, which is an important factor to cause seizure and epilepsy because of their pathophysiologic conditions and inclination to falls. Brain tumors are a recognized risk factor for epilepsy in elderly. Frequently associated with seizures are low grade well-differentiated tumors, cortical location, particularly in the temporal, frontal and motor or sensory cortices. The most common types of brain tumors in elderly are gliomas, meningiomas and metastases. Episodes of chronic seizure itself and the result of psychosocial disruption of patients' lifestyles significantly impair patients' quality of life. Poor cognitive outcome is generally associated with an early onset and a long duration of the epilepsy, with poor seizure control. Epilepsy in dementia has significant consequences on the prognosis of the underlying dementia. Additionally, old adults with a seizure are vulnerable to the adverse effects of medications. OSA affects one third epilepsies and is associated with a variety of medical comorbidities. OSA is particularly prevalent seen in elderly, male and in those who have seizures during sleep. Treatment with CPAP significantly reduces the frequency of interictal spikes on EEG-PSG studies, enhances seizure control, and improves quality of life in patients with OSA and epilepsy.

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