



Seizures in the elderly: Impact on mental status, mood, and sleep[☆]

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ABSTRACT

Comorbidities of epilepsy have not been well explored in the elderly. Herein, we examined mental status, mood, and sleep in elderly patients with epilepsy, compared with age- and gender-matched community controls without epilepsy from the Einstein Aging Study. Testing included a mental status test, the Blessed Information Memory and Concentration (BIMC) test; Prime-MD Patient Health Questionnaire (PHQ) Depression and Anxiety Modules; and Medical Outcomes Study Sleep Scale. Persons with epilepsy ($n = 31$) had higher mean BIMC scores than controls ($n = 31$, BIMC 6.3 vs. 1.2, $P < 0.0001$). Mean PHQ Depression scores were higher for cases than controls, indicating more depressive symptoms (4.2 vs 0.8, $P = 0.006$); six cases (18%) and no controls met screening criteria for depression. Mean PHQ Anxiety scores were also higher for cases than controls (3.7 vs 0.0, $P = 0.001$). Cases had poorer sleep scores in the categories of somnolence ($P = 0.009$) and shortness of breath/headache ($P = 0.021$). Thus, comorbidities of epilepsy in this elderly population included decreased mental status, a higher prevalence of depression and anxiety, and poorer sleep health when compared with age-mates without epilepsy. Mental status impairment was not related to antiepileptic medication or mood disturbance. Further investigation will explore these associations prospectively.

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1. Introduction

Elderly persons experience epilepsy at age-specific rates higher than those of any other age group [1,2]. They may be especially vulnerable to the sequelae of seizures and their treatment, and may experience worsened health-related quality of life as compared with their age-mates [3–5]. Furthermore, well-recognized comorbidities of epilepsy such as depression, anxiety, and sleep disorders [6–9] occur with increasing frequency with advancing age [10–12] and merit examination in this special population [13]. Few studies have examined these comorbidities of epilepsy in the elderly. Furthermore, although late-stage dementia is an identified risk factor for seizures and epilepsy [14,15], the association in the opposite direction is less clear, and the issue of cognitive and brain health in the elderly with epilepsy has recently been described as neglected and poorly understood [16].

Herein we explored the association between epilepsy, mental status impairment, and other selected comorbidities in our elderly, community-dwelling population, also addressing the potential

contribution of antiepileptic medication. We hypothesized that the prevalence of mental status dysfunction, sleep disturbance, and mood disorders would be increased in persons with epilepsy in comparison with their age-mates free of seizures. Confirmation of these comorbidities in elderly persons with epilepsy would have important implications in clinical practice. It would imply that clinicians who treat the elderly with epilepsy should be vigilant to the presence of these other important conditions; particularly as sleep and mood disorders are treatable. Furthermore, if mental status impairment in epilepsy is a presenting feature of dementia, earlier detection may contribute to improved outcome. Finally, demonstration of comorbidities creates opportunities to explore the mechanisms that link these disorders.

2. Methods

2.1. Subjects

Subjects were recruited from two sources serving the same community in the Bronx: the Epilepsy Management Center at Montefiore Medical Center, and the Einstein Aging Study (NIH PO1 AG03949 (RBL)). The Epilepsy Management Center includes the Faculty Practice and the Seizure Clinic. The Einstein Aging Study (EAS) is a longitudinal study of systematically recruited community-dwelling elderly adults. Subjects are followed annually

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with medical and epidemiological histories and neuropsychological testing, as well as general medical and neurological examinations. This study was performed with the approval of the Montefiore Medical Center (MMC) Institutional Review Board and the Albert Einstein College of Medicine (AECOM) Committee on Clinical Investigations (CCI). All subjects signed informed consent.

Persons with epilepsy (cases) were recruited from both the Epilepsy Management Center and the Einstein Aging Study. All cases were age 65 or older and had a diagnosis of epilepsy confirmed by an epileptologist (S.R.H.), by a review of clinical records applying standard criteria [17].

Controls were recruited from the EAS, did not have a history of seizures, and were matched by gender and age (within 5 years) to the cases. Epilepsy was the only basis for excluding individuals from the control group. The EAS controls chosen for the present study are representative of the overall EAS study population. EAS subjects overall take 2.75 ± 2.50 medications; the EAS controls in this study take 3.03 ± 1.90 medications. Rates of the five most common medical conditions among the EAS control group (hypertension, diabetes, cancer, myocardial infarction, claudication) are similar to rates in the overall EAS study. Both cases and controls were free of DSM-IV-defined dementia [18], and had scores on the Blessed Information Memory and Concentration (BIMC) test of less than 8 [19]. The data were prospectively collected, with the current analysis as a planned post hoc analysis.

2.2. Definition of outcomes

2.2.1. Mental status

The BIMC test was used to measure mental status [20]. Items missed or answered incorrectly are scored so that higher scores indicate increasing mental status impairment. A score of 4 or greater on the BIMC suggests cognitive dysfunction, and scores of 8 or greater indicate dementia or delirium [19]. The BIMC was used because it has long been employed in the EAS. The instrument was originally selected because of its demonstrated correlation with pathological markers of dementia. The BIMC correlates very highly with the more widely used Mini Mental Status Examination (MMSE) [21].

2.2.2. Depression and anxiety

Modules from the Patient Health Questionnaire were used to assess depression and anxiety [22,23]. These self-report questionnaires are widely used and specifically validated in the elderly and in persons with a broad range of medical comorbidities [23,24]. These modules assess the frequency of specific symptoms of depression and anxiety; higher scores indicate greater symptomatology. The 9-item PHQ depression screener has an empirical cut score of 15 or greater, which identifies DSM-IV-defined Major Depressive Disorder of at least moderate severity. The Prime-MD screener for anxiety is a three-item assessment questionnaire. A positive endorsement to any one of the three items is defined as a positive screen for anxiety. Although disease-specific psychiatric screening tools are available for epilepsy [25], they are designed for use in persons with epilepsy and not suitable for comparing cases with epilepsy and controls. We chose instruments that were validated in the elderly that would be more likely to operate similarly in both the case and control samples. The PHQ tools are validated in the elderly and robust in face of a number of concomitant illnesses [23,24].

2.2.3. Sleep disturbances

The Medical Outcomes Study (MOS) Sleep Scale was used to examine various aspects of sleep [26]. The MOS measures sleep patterns and disturbances on seven different scales. Answers are

based on a retrospective assessment over the previous 4 weeks, and each domain is computed on a range of 0–100, with a higher score more indicative of the aspect being measured.

2.2.4. Epilepsy variables

In the intake interview, seizure frequencies in the prior month and the prior 6 months were ascertained. Those who experienced no seizures during the prior 6 months were considered “well controlled.” Current antiepileptic drugs (AEDs) were recorded. Epilepsy was classified according to International League Against Epilepsy guidelines [17].

2.3. Statistical analysis

Scores on the BIMC, Prime MD PHQ Depression and Anxiety Scales, and MOS Sleep Scale were treated as continuous variables. Epilepsy control was treated as a dichotomous variable (well controlled vs not well controlled) as were AEDs (0 or 1 vs >1). Differences in mean scores for continuous variables were tested for significance using Student's *t* test for paired samples (case-control comparison), independent samples (case comparison) if assumptions were met, or Mann-Whitney *U* test for nonparametric evaluation [27]. All analyses were computed using SPSS software [28].

3. Results

Data were analyzed for 62 subjects, 31 epilepsy cases and 31 controls. Demographic data are summarized in Table 1. Groups did not differ in age or gender distribution. The mean age for subjects overall was 74.6 ± 6.4 . Sixty-seven percent of the subjects were female. Degree of independent living for cases and controls is indicated. Cases were significantly more likely than controls to live with a child rather than alone or with a spouse ($P < 0.005$).

3.1. Epilepsy etiology, classification, and control

Epilepsy was localization related in all cases; none of the cases had a primary generalized epilepsy syndrome. Thirteen subjects (42%) had remote symptomatic epilepsy, including five subjects with stroke and four subjects each with posttraumatic epilepsy and tumor/vascular anomalies. For 18 subjects (58%) no epilepsy etiology was identified, and these cases were considered idiopathic/cryptogenic. Three of these subjects had been diagnosed with mild cognitive impairment (MCI) subsequent to this study.

Age at epilepsy onset ranged from 6 to 85 years, and duration ranged from 2 to 63 years. Mean/median age at epilepsy onset was 51 years/58 years ± 20 years. Thirteen percent of subjects developed epilepsy prior to age 21. Twenty-five percent of subjects experienced epilepsy onset by age 32, and 50% by age 58. More than 60% of the cases had had epilepsy for >10 years.

Forty-six percent of cases with epilepsy were currently well controlled, whereas 54% had experienced at least one seizure during the 6 months. Mean seizures in the month prior to testing was 0.5, and the median was 0.

Antiepileptic medication use is indicated (Table 1). Seventy-five percent of cases were receiving monotherapy with one AED; nearly half of these were being treated with a second-generation agent (lamotrigine or levetiracetam). Control subjects were not receiving AED therapy for other indications.

3.2. Mental status

Mean BIMC for the group was 3.82 ± 5.1 , and the median 2.0 (interquartile range: 2.0–5.3). Median BIMC for cases with epilepsy was 5.0, as compared with 1.0 for controls (Table 2). Cases with

Table 1
Characteristics of the study population.

	Cases	Controls	Significance, <i>P</i>
Mean age, years	72.8 ± 7.1	76.6 ± 5.2	NS
Gender distribution (M/F)	34%/66%	34%/66%	NS
Living arrangement			
Lives alone	43%	53%	
Lives with spouse	36%	43%	
Lives with children	18%	4%	<0.005
Has home health aide	3%	0	
Current number of AEDs		N/A	
0	3%		
1	75%		
2	22%		
>2	—		
AED in subjects receiving monotherapy:		N/A	
Phenytoin	32%		
Carbamazepine	18%		
Levetiracetam	27%		
Lamotrigine	18%		
Phenobarbital	5%		

Table 2
Cognitive function.

	Cases	Controls	Significance, <i>P</i>
Mean BIMC score	6.25 ± 6.0	1.23 ± 1.3	<0.0001 ^a
Median BIMC score	5.0	1.0	
Cases only			
Mean BIMC score by number of AEDs			
0–1	6.23 ± 5.0		
2	8.5 ± 9.8 ^b		
Mean BIMC score by seizure control			
Well controlled	6.9 ± 6.2		
Poorly controlled	7.2 ± 7.4 ^b		

^a By Mann–Whitney *U* test for nonparametric data^b Within-column comparisons not significant.

epilepsy had significantly worse BIMC scores than controls (Mann–Whitney *U* test $P < 0.0001$). When presence of depression or anxiety was controlled for, BIMC scores remained significantly worse for persons with epilepsy than for controls. Among persons with epilepsy, BIMC scores were not significantly associated with number of AEDs (0 or 1 vs 2) or degree of seizure control (Mann–Whitney *U* test n.s.).

3.3. Depression and anxiety

Mean Prime–MD Depression scores were significantly higher for cases (4.2 ± 5.4) than controls (0.8 ± 1.8) ($P = 0.006$), with 6 of 31 cases (18%) and no controls meeting screening criteria for depression (Table 3). Among cases, subjects with poor seizure control had

Table 3
Mood and sleep disturbance.

	Cases	Controls	Significance, <i>P</i>
Prime MD Depression	4.2 ± 5.4	0.8 ± 1.8	0.006
Prime MD Anxiety	3.7 ± 4.1	0	<0.0001
MOS sleep scales			
Shortness of Breath	13.1 ± 23.6	3.3 ± 7.6	0.034
Somnolence	38.4 ± 31.0	22.7 ± 13.9	0.013
Sleep Disturbance	22.8 ± 26.7	26.7 ± 12.9	0.386
Sleep Adequacy	75.0 ± 32.2	63.5 ± 25.0	0.139
Sleep Disturbance	22.8 ± 26.6	26.7 ± 12.9	0.386
Sleep Problems (6 items)	25.1 ± 24.5	24.4 ± 12.4	0.885
Sleep Problems (9 items)	25.7 ± 22.8	25.0 ± 10.1	0.879

a significantly higher mean depression score (5.57 ± 5.4) than subjects with well-controlled seizures (0.38 ± 1.0) ($P < 0.0001$).

Mean Prime–MD Anxiety Scores were also significantly higher for cases (3.73) than controls (0.0) ($P < 0.0001$), although no subject met screening criteria for anxiety disorder (Table 3). Within cases, mean scores were higher but did not significantly differ for poorly controlled (5.75 ± 8.9) versus well-controlled (1.8 ± 3.1) epilepsy ($P = 0.116$).

3.4. Sleep disorders

Of the seven domains measured by the MOS Sleep Scales (Adequacy, Disturbances, Somnolence, Snoring, Shortness of Breath/Headache, Other problems Index 1 and 2), cases demonstrated significantly poorer sleep scores than controls in the categories of Somnolence ($P = 0.009$) and Shortness of Breath/Headache ($P = 0.021$) (Table 3). Among cases, poor seizure control was associated with shortness of breath/headache ($P = 0.006$) and general disturbances ($P = 0.047$). Mental status was not significantly different for subjects with and without significant somnolence or shortness of breath ($P = 0.34$).

4. Discussion

There is increasing recognition that elderly patients with epilepsy represent a unique population with particular needs [16,29,30]. Most studies in epilepsy have not focused on this age group, and few have examined multiple comorbidities. Herein, we evaluated several well-known comorbidities of epilepsy the prevalence of which also increases with advancing age.

In our sample of community-dwelling elderly, mental status as measured by the BIMC was significantly impaired in cases with localization-related epilepsy as compared with controls without epilepsy. As a cross-sectional finding, these results are consistent with previous cross-sectional studies specifically addressing cognition in the elderly population with epilepsy [29,31–33]. The relationship of cognitive dysfunction to duration of epilepsy remains unclear. A number of prospective studies have demonstrated cognitive decline in association with chronic epilepsy [34,35], although in a review of all available longitudinal studies performed prior to 2004 [36], none had focused on the elderly, and 12 of 20 studies supported the finding of cognitive decline, whereas 8 did not. In one recent longitudinal study of cognitive functioning in elderly persons with partial epilepsies, overall cognitive deficit appeared to remain fairly stable over time [37], although executive dysfunction progressed.

In our study, cognitive deficits in the elderly with epilepsy were not associated with seizure burden. In contrast, studies of the general epilepsy population suggest that a longer duration of epilepsy or poor seizure control is significantly related to cognitive decline [38–41]. Seizure control over the last 6 months may not adequately measure lifetime seizure burden, particularly in the elderly; we are therefore not willing to exclude the possibility that seizures cause cognitive impairment. Better measures of seizure burden and cognitive status, particularly in a longitudinal context, might reveal associations not detected here.

Polypharmacy has been implicated as a risk factor for cognitive impairment; in prior studies, the number of AEDs was negatively associated with cognition, both in comparison to healthy controls [31] and even in comparison to older adults with mild cognitive impairment taking anticholinesterase inhibitors [32]. In these studies, the percentage of patients taking monotherapy ranged from 52% to 57%. In our population, the number of AEDs was not significantly associated with poorer performance on the BIMC. This may in part reflect the large proportion (75%) of subjects taking

monotherapy, and the high prevalence of newer antiepileptic agents, which may produce less cognitive impairment than older agents [42]; these agents are better tolerated, especially in the elderly [43]. However, as the controls were not taking AEDs, the effects of AEDs may have contributed to the difference between the groups. The presence of cognitive impairment in cases may explain the differences in living arrangements between cases and controls. Although all subjects were community dwellers, a significantly larger percentage of cases with epilepsy lived less independently than controls.

Psychiatric comorbidities, particularly mood disturbances such as depression and anxiety disorders, are associated with epilepsy [7,44–48] and increase in prevalence with advancing age [11,12]. In our study, elderly persons with seizure disorders suffered from elevated rates of depression and anxiety as compared with controls. Several measures have revealed that depression or other psychological stress may be the strongest predictor of health-related quality of life for persons with epilepsy [49], highlighting the importance of these comorbidities in the elderly population with epilepsy. Furthermore, antiepileptic medications have the potential to produce or worsen mood disorders [50,51], and in our study, it is difficult to separate the effect of medication from the effect of epilepsy. However, the elderly may be particularly sensitive to these medication effects, underscoring the need to evaluate mood in this population.

The overall rate of depression and anxiety in our study appears lower than other reports of depression in epilepsy; this may be related to the relatively long duration of epilepsy in our cases, as later age at onset of epilepsy appears to be a risk factor for mood disorders [52].

Sleep health is particularly important to address in the elderly with epilepsy, as seniors in the general population have a higher degree of sleep disturbance than younger individuals [53,54]. Sleep disturbance is an increasingly noted comorbidity of epilepsy [8]. Sleep disorders such as insomnia and excessive daytime sleepiness lower quality of life measures for persons with epilepsy [55], and sleep deprivation is considered a seizure precipitant in numerous reports [56–59]. Obstructive sleep apnea has recently been linked to increased seizure frequency in the elderly [60]. However, to our knowledge, general sleep disturbance has not been previously investigated in the elderly with epilepsy. We found a strong correlation between reported sleep health, presence of epilepsy, and current degree of seizure control. Our elderly subjects with epilepsy had significantly elevated scales measuring sleep somnolence and shortness of breath as compared with cases. Although previously reported [54,61], sleep disturbance in our study was not accounted for by depressed mood. Poor sleep may also contribute to cognitive decline [62,63], although in our study, sleep disturbance was not associated with cognitive impairment. It is possible that improving sleep health in this age group will have a positive effect on both seizure control and cognition.

Our study has a number of limitations. It is a cross-sectional study and, so, cannot determine the temporal relationships between epilepsy and the examined comorbidities. Planned prospective studies will address these concerns. In addition, though our cases with epilepsy and controls were matched for age and sex and drawn from the same community, it is possible that selection bias influenced study results. Our cognitive assessment was limited to an excellent test of mental status, which correlates very highly with the better known Mini Mental State Examination [21]. It is possible that a battery of more robust neuropsychological measures would reveal differences not apparent here. We could not fully control for medication effects, including the potential effects of antiepileptic medication on cognition and mood. Finally, seizures in more than half of the cases with epilepsy were not well controlled; this sample may be more refractory to treatment than

the general epilepsy population. This finding is likely accounted for by the selection of cases from an epilepsy tertiary care center. The applicability of our results to the elderly with epilepsy followed in general neurology practice should be explored.

The elderly with epilepsy are not a homogeneous population. Prior studies of epilepsy have demonstrated that significant differences exist between community dwellers and nursing home residents [30]. Although epilepsy comorbidities such as cognitive impairment may be expected to be high in an assisted living population, the subjects in our study represent a community-based sample; as such, the findings are perhaps even more significant. Future planned studies will use a more extensive cognitive assessment targeted to specific cortical regions (i.e., frontal lobe executive function) to further enhance our understanding of the relationship between cognition and epilepsy.

Thus, our results confirm that the elderly with epilepsy have numerous clinically significant comorbidities, including mental status impairment, mood disturbance, and poorer sleep health. These comorbidities may impact independent living and quality of life. In the treatment of elderly patients with epilepsy, maintaining functional independence is an important goal. It is therefore important for treating clinicians to be aware of these common comorbidities and address them. It is also important to determine if the prominent mental status impairment is a consequence of epilepsy or of its treatment so that management strategies that optimize cognitive function can be developed.

Ethical approval

The authors confirm that we have read the Journal's position on issues involved in ethical publication, and affirm that this report is consistent with those guidelines.

Conflict of interest statement

Dr. S.R. Haut serves on the Speaker's Bureau of UCB Pharma and the advisory boards of UCB Pharma and Abbott. She has served as a paid consultant for King, Jazz, and Genactis. Dr. R.B. Lipton has served as a paid consultant for, and received grant support from, Pfizer and Endo. None of the other authors have any conflicts of interest to disclose.

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