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Recurrent Seizures in Patients with Dementia: *Frequency, Seizure-types and Treatment Outcome*

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Abstract

Introduction—Patients with a primary neurodegenerative disorder associated with cognitive impairment are at increased risk for epilepsy. The rationale for the present study is to characterize seizure-type(s), etiological diagnosis of dementia, electroencephalogram (EEG) and imaging findings, and response to antiepileptic drugs (AED) in these individuals.

Methods—A retrospective study was performed identifying patients in the Mayo Alzheimer Disease Patient Registry (ADPR) and Alzheimer Disease Research Center (ADRC) who were classified as having dementia and epilepsy from 1986 to 2006. Multiple clinical parameters were extracted from patient charts and evaluated to characterize the primary neurodegenerative disorder and seizure outcomes.

Results—Sixty three of the 1,738 ADPR and ADRC patients (3.6%) had epilepsy. Twenty four of the sixty three patients were excluded because of insufficient information regarding their epilepsy. The remaining thirty nine patients were analyzed. Twenty-eight of the 63 patients (72%) experienced complex partial seizure activity. An MRI head was performed in 35 patients (90%). Fourteen patients (36%) had MRI-identified structural lesions that included remote stroke or prior intracerebral hemorrhage. An EEG was obtained in 29 patients (74%). Fifteen patients (38%) had EEG-identified epileptiform discharges. Overall, it was found that seventy nine percent had an excellent response to AED therapy. Approximately one-third of the patients had dose-related side effects from an AED.

Discussion—The present study indicated that most individuals with the comorbidity of epilepsy and dementia have complex partial seizures that may be adequately controlled on AED therapy. The long-term effect of seizure activity on the neurodegenerative disorder is unknown.

Keywords

epilepsy- dementia- Alzheimer's disease

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1. Introduction

The epilepsies increase in prevalence with age, and even more so in the demented population. As average life span continues to lengthen, the elderly population (>65 years of age) continues to grow as well (Hauser 1997, Mendez and Lim 2003). This, in turn, leads to increasing numbers of people who develop dementia primarily from neurodegenerative and vascular causes. Previous studies have shown that eight percent to 22% of patients with Alzheimer's disease (AD), the most common etiology for dementia, have at least one unprovoked seizure (Mendez et al. 1994, Mendez and Lim 2003, Amatniek et al. 2006). Furthermore, patients with AD and other types of dementias are at 5 – 10 fold increased risk of epilepsy compared to age matched controls (Hauser 1986, Hesdorffer et al. 1996, Mendez and Lim 2003).

The rationale for the present study is to evaluate the frequency of seizure activity and clinical characteristics in individuals with a progressive neurodegenerative disorder associated with a cognitive impairment. This included analysis of seizure types, neurodiagnostic findings, treatment outcome, and adverse antiepileptic drug (AED) reactions.

2. Methods

A retrospective chart review was performed identifying patients in the Mayo Alzheimer Disease Patient Registry (ADPR) and Alzheimer Disease Research Center (ADRC) who were classified as having dementia and epilepsy from 1986 to 2006. The databases that included active (patients seen in the clinic within the last two years) and inactive (patients not seen in the clinic within the last two years) were searched with the keywords 'seizure' or 'epilepsy'. The total number of patients in the databases was one thousand seven hundred and thirty-eight. Patients with epilepsy were included in the present study and analyzed by basic statistical methods (means, proportions) using JMP software, version 6.0 (SAS Institute, Cary, NC; www.jmp.com). A single investigator (SCR) reviewed all charts and abstracted the appropriate information. The study was evaluated and approved by the Mayo Foundation Institutional Review Board.

Treatment outcome was defined via a modified Engel classification system. The following categories were used: (I) Seizure free, (II) greater than 95% reduction in seizure frequency and less than 3 seizure's per year, (III) 80% - 94% reduction in seizure frequency, (IVa) 50% to 79% reduction in seizure frequency, and (IVb) less than 50% reduction in seizure frequency. This was determined from patient charts over last two years, or if deceased, five years prior to death.

3. Results

Sixty three of the 1,738 active and inactive patients (3.6%) in the ADPR and ADRC databases had recurrent seizures. Twenty four of the 63 patients were excluded because of insufficient information regarding their epilepsy. The remaining 39 patients with dementia and seizures were included in the present series. The mean age was 76.9 years (range, 52 to 100 years). There were 21 females and 18 males. The mean age of dementia onset was 71 years (range, 48 to 91 years). The mean age of seizure onset was 62 years (range, 1 to 86 years). The neurodegenerative diseases associated with dementia included mild cognitive impairment (MCI) (n=10), AD (n=9), vascular dementia (n=6), and Lewy body disease (n=5). The stage of neurodegenerative disease beyond the differentiation between MCI and AD was difficult to ascertain as many of the follow-up outpatient visits were performed by primary care physicians rather than neurologists, and detailed neurological and neuropsychological assessments were lacking in the clinical notes. Twenty-eight patients (72%) had recurrent complex partial seizures and 15 patients (52%) had generalized tonic-clonic seizures (Table 1). An MRI head

was performed in 35 patients (90%). Fourteen patients (36%) had MRI-identified structural lesions that included remote stroke (n=12) or prior intracerebral hemorrhage (n=2). An EEG was obtained in 29 patients (74%). Fifteen patients (38%) had EEG-identified epileptiform discharges. The EEG in these individuals most commonly revealed unilateral or bilateral spike or sharp wave discharges. Thirty-one patients (79%) became seizure-free or had a greater than 95% reduction of seizure frequency and less than three seizures per year with AED therapy. One patient (2.6%) had a 50% to 79% reduction of seizure frequency, and three individuals (7.7%) had less than a 50% reduction of seizure frequency with AED medication (Table 1). The AED medications administered included phenytoin (38.5%), valproic acid (17.9%), carbamazepine (15.4%), gabapentin (10.3%), phenobarbital (2.6%), and clonazepam (2.6%). Twenty-eight patients (72%) received one AED medication and 11 patients (28%) were on two or more AED medications. Twelve patients (31%) had dose-related adverse effects. The most common medication related symptom was drowsiness in eight patients (21%). The remaining 27 patients (69%) had no drug-induced adverse effects. No patients had idiosyncratic or life-threatening AED side effects.

4. Discussion

The increased risk of newly diagnosed epilepsy in the elderly population has been confirmed (de la Court et al. 1996). Dementia occurs in three to six percent of individuals over 60 years of age (Rocca et al. 1990, Wang et al. 2000). The most common neurological illness with dementia as a prominent feature is AD (Schoenberg et al. 1987). The association of recurrent and unprovoked seizures in patients with dementia has been established (Amatniek et al. 2006, Hesdorffer et al. 1996). The frequency of epilepsy in the present series is lower than what has been reported previously. This may be due to multiple reasons including the fact that half of patients in the present sample were classified as having MCI. The milder degree of cognitive impairment and presumed accompanying neuronal loss may be less epileptogenic. There may have also been under reporting of seizure activity. As noted above, many of the clinical follow-up appointments were done by primary care physicians. It is likely that a neurological review of systems was not routinely performed during those visits that, for example, would illicit a history of complex partial seizures. Some of the earlier studies assessed only patients who developed seizures after or near the time of onset of the cognitive deterioration (Mendez et al. 1994, Mendez and Lim 2003, Amatniek et al. 2006). The present study included some patients who began having seizures before the onset of dementia.

The putative epileptogenic mechanism in patients with combined recurrent seizures and a progressive neurodegenerative disorder may relate to the findings of neuronal loss and gliosis in selected regions such as the medial temporal lobe. Hippocampal neuronal loss and increased excitotoxicity with abnormal mossy fiber sprouting may be identified in partial epilepsies (Avoli et al. 2005). The pathological findings underlying the temporal lobe may be similar in patients with mesial temporal sclerosis associated with partial epilepsy and the clinical entity entitled "hippocampal sclerosis dementia" (Leverenz et al. 2002, Velez-Pardo 2004). Hippocampal sclerosis is also frequently associated with frontotemporal lobar degeneration (FTD) (Blass et al. 2004, Hatanpaa et al. 2004, Josephs et al. 2006). However, the presence of hippocampal neuronal loss in patients with a progressive neurodegenerative disorder may not indicate an increased seizure tendency. A community-based study of dementia related to hippocampal sclerosis showed no increase in the incidence of seizure activity in these patients (Leverenz et al. 2002). In a previous study only one patient of eighteen with FTD and hippocampal sclerosis had seizures (Josephs et al. 2006). Other factors like mossy fiber sprouting to increase excitotoxicity may be necessary for the development of epileptogenesis (Nadler 2003). Velez-Pardo et al. reported an association of the presenilin-1 mutation of familial AD to hippocampal neuronal loss and epilepsy (Velez-Pardo et al. 2004).

Our study does not address these mechanistic aspects, but instead characterizes the clinical profiles of patient's with these comorbidities. The most striking finding, in the authors' opinion, is the excellent treatment outcome. Clinically, it is satisfying to predict that these patients will do well with AED's. Although the limited sample size reduces the power of this result, it is somewhat similar, or slightly higher, to the well known treatment outcome of the epilepsy population as a whole. This has been reported as 60% to 70% of patients become seizure-free on AED therapy (Sander 1993, Brodie et al. 1996, Mattson and Cramer 1997, Kwan and Brodie 2000). Prior to this study, it was unclear whether the dementia population would have higher rates of drug-resistant epilepsy.

Phenytoin was the most frequently used AED in the patients of the present study. Past studies have also reported that phenytoin is the most frequently used AED in nursing home and demented populations (Mendez et al. 1994, Lackner et al. 1998, Garrard et al. 2000). The frequency of dose-related AED side effects reported in this study is similar to the general epilepsy population, which can has been reported up to 40% or higher (Sander 2004). The calculated AED dose-related side effects in the present study (30%) maybe an underestimate due to patient under reporting, lack of physician inquiry regarding side effects, or omission of this information from the medical charts. In our study, it was not possible to accurately quantify rates of dementia progression and correlate that to seizure burden and/or AED cognitive side effects, such as abnormal mentation, somnolence etc. Although the long-term effect of seizure activity on the neurodegenerative disorder is unknown, one could speculate that treating the epilepsy is beneficial to the patient.

Complex partial was the most frequent seizure type in this group of patients. A study by Mendez et al. on AD patients found generalized tonic-clonic to be the most frequent seizure type (Mendez et al. 1994). In either case, it may be prudent to ask family and / or caregivers during initial or follow-up evaluations regarding clinical events suggestive of seizure activity. If there is suspicion, then obtaining an EEG may help guide management. If clinical suspicion is high, and there is epileptiform activity on EEG, our study suggests that the patient will likely have a good response to AED therapy and experience minimal side effects.

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References

- Amatniek JC, Hauser WA, DelCastillo-Castaneda C, Jacobs DM, Marder K, Bell K, Albert M, Brandt J, Stern Y. Incidence and predictors of seizures in patients with Alzheimer's disease. *Epilepsia* 2006;47(5):867–872. [PubMed: 16686651]
- Avoli M, Louvel J, Pumain R, Kohling R. Cellular and molecular mechanisms of epilepsy in the human brain. *Prog Neurobiol* 2005;77(3):166–200. [PubMed: 16307840]
- Blass DM, Hatanpaa KJ, Brandt J, Rao V, Steinberg M, Troncoso JC, Rabins PV. Dementia in hippocampal sclerosis resembles frontotemporal dementia more than Alzheimer's disease. *Neurology* 2004;63:492–497. [PubMed: 15304580]
- Brodie MJ, Dichter MA. Antiepileptic drugs. *N Engl J Med* 1996;334(3):168–175. [PubMed: 8531974]
- de la Court A, Breteler MMB, Meinardi H, Hauser WA, Hofman A. Prevalence of epilepsy in the elderly: the Rotterdam Study. *Epilepsia* 1996;37(2):141–147. [PubMed: 8635424]
- Garrard J, Cloyd JC, Thomas L, Lackner T, Graves N, Leppik I. Factors associated with antiepileptic drug use among elderly nursing home residents. *J Gerontol A Biol Sci Med Sci* 2000;55:M384–392. [PubMed: 10898255]

- Hatanpaa KJ, Blass DM, Pletnikova O, Crain BJ, Bigio EH, Hedreen JC, White CL, Troncoso JC. Most cases of dementia with hippocampal sclerosis may represent frontotemporal dementia. *Neurology* 2004;63:538–542. [PubMed: 15304590]
- Hauser WA, Morris ML, Heston LL, Anderson VE. Seizures and myoclonus in patient's with Alzheimer's Disease. *Neurology* 1986;36:1226–1230. [PubMed: 3092131]
- Hauser, WA. Epidemiology of seizures in the elderly. In: Rowan, AJ.; Ramsey, RE., editors. *Seizures and Epilepsy in the elderly*. Boston: Butterworth-Heinemann; 1997. p. 7-20.
- Hesdorffer DC, Hauser WA, Annegers JF, Kokmen E, Rocca WA. Dementia and adult onset unprovoked seizures. *Neurology* 1996;46:727–730. [PubMed: 8618673]
- Josephs KA, Whitwell JL, Jack CR, Parisi JE, Dickson DW. Frontotemporal Lobar Degeneration Without Lobar Atrophy. *Arch Neurol* 2006;63:1632–1638. [PubMed: 17101834]
- Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342(5):314–319. [PubMed: 10660394]
- Lackner T, Cloyd JC, Thomas LW, Leppik I. Antiepileptic drug use in nursing home residents: effect of age, gender, and comedication on patterns of use. *Epilepsia* 1998;39:1083–1087. [PubMed: 9776329]
- Leverenz JB, Agustin CM, Tsuang D, Peskind ER, Edland SD, Nochlin D, DiGiacomo L, Bowen JD, McCormick WC, Teri L, Raskind MA, Kukull WA, Larson EB. Clinical and neuropathological characteristics of hippocampal sclerosis: a community-based study. *Arch Neurol* 2002;59:1099–1106. [PubMed: 12117357]
- Mattson, RH.; Cramer, J. The choice of antiepileptic drugs in focal epilepsy. In: Wyllie, E., editor. *The treatment of epilepsy: principles and practice*. Baltimore: Williams & Wilkins; 1997. p. 771-778.
- Mendez MF, Catanzaro P, Doss RC, Arquello R, Frey WH. Seizures in Alzheimer's disease: clinicopathologic study. *J Geriatr Psychiatry Neurol* 1994;7(4):230–233. [PubMed: 7826492]
- Mendez M, Lim G. Seizures in elderly patients with dementia: epidemiology and management. *Drugs Aging* 2003;20(11):791–803. [PubMed: 12964886]
- Nadler JV. The recurrent mossy fiber pathway of the epileptic brain. *Neurochem Res* 2003;28(11):1649–1658. [PubMed: 14584819]
- Rocca WA, Bonaiuto S, Lippi A, Luciani P, Turtu F, Cavarzeran F, Amaducci L. Prevalence of clinically diagnosed Alzheimer's disease and other dementing disorders: a door-to-door survey in Appignano, Macerata Province, Italy. *Neurology* 1990;40(4):626–631. [PubMed: 2320236]
- Sander JW. Some aspects of prognosis in the epilepsies: a review. *Epilepsia* 1993;34:1007–1016. [PubMed: 8243349]
- Sander JW. The Use of Antiepileptic Drugs – Principles and Practice. *Epilepsia* 2004;45:28–34. [PubMed: 15315513]
- Schoenberg BS, Kokmen E, Okazaki H. Alzheimer's disease and other dementing illnesses in a defined United States population: incidence rates and clinical features. *Ann Neurol* 1987;22(6):724–729. [PubMed: 3435081]
- Velez-Pardo C, Arellano JJ, Cardona-Gomez P, Jimenez Del Rio M, Lopera F, De Felipe J. CA1 hippocampal neuronal loss in familial Alzheimer's disease presenilin-1 E280A mutation is related to epilepsy. *Epilepsia* 2004;45(7):751–756. [PubMed: 15230697]
- Wang W, Wu S, Cheng X, Dai H, Ross K, Du X, Yin W. Prevalence of Alzheimer's disease and other dementing disorders in an urban community of Beijing, China. *Neuroepidemiology* 2000;19(4):194–200. [PubMed: 10859498]
- www.jmp.com

Table 1

Seizure Outcome in Patients with Cognitive Disorders	
modified Engel Classification *	percentage of patients
Class I & II	79%
Class III	10%
Class IVa	3%
Class IVb	8%
Seizure Classification in Patients with Cognitive Disorders	
seizure type	number of patients
Complex partial	28
Tonic clonic	15
Simple partial	5
Atypical absence	1
Myoclonic	3
Unknown	1

* (I) Seizure free, (II) greater than 95% reduction in seizure frequency and less than 3 seizure's per year, (III) 80% -94% reduction in seizure frequency, (IVa) 50% to 79% reduction in seizure frequency, and (IVb) less than 50% reduction in seizure frequency.