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# Accepted Manuscript

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# Epilepsy in Neuropathologically Verified Alzheimer's Disease

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Highlights

- A well-defined study group of 64 subjects with AD was assessed
- 17% of the 64 subjects with AD had a history epilepsy
- Subjects with AD and epilepsy were significantly younger

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Abstract

Purpose: Subjects with Alzheimer's disease (AD) have been shown to be at a higher risk for epilepsy. The vast majority of the previous studies have not included a full neuropathological examination.

Methods: The objective of this study was to assess the prevalence of epilepsy and clinicopathological characteristics in a well-defined study group of 64 subjects with AD. We evaluated the clinicopathological findings in 64 subjects (mean age at death 85±8.6 years) from a longitudi-nal study cohort of patients with dementia.

Results: Eleven out of the 64 subjects (17%) had a history of epilepsy, which is comparable to previous studies. The subjects with AD and epilepsy were significantly younger at the time of AD diagnosis and at the time of hospitalization. In addition, their duration of AD was longer. Concomitant neuropathology in addition to AD was common in both groups and the ApoE genotypes did not differ significantly between the groups.

Conclusion: The strength of this study is a thorough neuropathological examination of all study subjects. Our findings support the previous literature regarding the prevalence of epilepsy in subjects with AD. We have shown that the subjects with AD and epilepsy differ significantly from the subjects without epilepsy.

Keywords: Alzheimer, dementia, epilepsy, autopsy, neurodegeneration

Number of tables 1
Number of figures 1
Number of references 12
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## Introduction

Alzheimer's disease (AD) is the most common cause for dementia and it is generally accepted that patients suffering from AD are at a higher risk for epilepsy than individuals without AD[1,2] and this association has been shown to be particularly strong in subjects with dementia onset at a young age[2]**.** One explanation is that the progression of a neurodegenerative disease, neurotrauma and events such as cerebrovascular stroke may trigger EP in the elderly population[3]. Therefore, the association between epilepsy and neurodegenerative dis-

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eases, especially AD, is being actively studied. Previous studies have shown that the incidence of EP is the highest in the persons aged more than 75 years[4]. It has been suggested that the appearance of epileptic seizures in patients with AD may be a marker for cortical neurodegeneration and for late stages of the disease process[5]. In the early stages of AD, seizures may reflect an aggressive progression of the disease or could be attributable to other factors such as susceptibility to hypersynchronous electrical activity[1]. Despite of the modern imaging modalities and proteomic analysis, a systematic neuropathological examination is still the golden diagnostic standard and especially valuable for assessing the concomitant pathology, which is often present in the brain of elderly subjects. The number of studies on the topic of epilepsy and AD including a full neuropathological investigation is unfortunately relatively small and this may lead to biased findings and conclusions. The purpose of this clinicopathological study was to characterize the neuropathological and clinical findings in a well-defined study group of aged AD subjects with and without epilepsy.

## Methods

The study population included 64 neuropathologically confirmed AD patients (6 male, 58 female) that were recruited into a longitudinal follow-up study of patients with dementia of Alzheimer's type from the geriatric department of Harjula Hospital in Kuopio, Finland. At baseline the patients fulfilled the clinical criteria for probable or possible AD defined by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[6]. The study was authorized by the Research ethics committee of the Kuopio University Hospital and Finnish National Authority for Medicolegal Affairs. All neuropathological examinations were performed at the department of Pathology of the Kuopio University Hospital by experienced neuropathologists between the years 1991 and 2001. The brains were weighed, evaluated for grossly detectable lesions and vessel abnormalities, perfused with and immersed in 10% buffered formalin for at least one week and cut in coronal slices of 1 cm thickness. Brain specimens were taken from 15 standard regions (frontal, temporal, parietal, precentral, occipital cortices, cingulate gyrus, striatum, basal forebrain including amygdala, thalamus, anterior and posterior hippocampus, midbrain including substantia nigra, pons including locus coeruleus, medulla oblongata, cerebellar vermis and cortex as well as from all macroscopically notable lesions), embedded in paraffin and cut into the 7 μm-thick sections. The sections were then stained routinely applying haematoxylin-eosin (H&E), Bielschowsky silver impregnation and immunohistochemistry for beta-amyloid, hyperphosphorylated tau and alpha-synuclein

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as described earlier[7]. AD-related pathology, i.e. neuritic plaques, were quantified in three cortical areas stained with Bielschowsky silver impregnation and all subjects were classified according to recommendations by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[8]. The clinical phenotype was obtained from the medical records by a neurologist and the ApoE genotype was available from all patients. The ApoE genotype was analyzed using polymerase chain reaction (PCR) as described earlier[9] with the genomic DNA being extracted from blood or brain tissue samples. The assesment of epilepsy was based on retrospective analysis of medical records. Epilepsy was assessed according to current ILAE recommendations and guidelines.

One-way ANOVA and Chi-Square Independence Test (SPSS statistics version 24) were conducted to compare group means and to determine the associations between AD+epilepsy and AD groups. Significance level $p<0.05$ was used.

Results

The demographic, neuropathological and clinical findings are summarized in table 1. There were statistically significant differences between means of the AD+epilepsy and AD groups in Age at the time of AD diagnosis ($F(1,59) = 5.632$, $p = .021$), in age at the time of hospitalisation ($F(1,58) = 5.468$, $p = .023$), and in duration of AD ($F(1,59) = 6.229$, $p = .015$) as determined by One-Way ANOVA. There were no statistically significant differences between means of the AD+epilepsy and AD groups in age at death or in brain weight in grams ($p = .182$ and $p = .256$, respectively). The load of vascular lesions did not differ between the groups. Patients in AD+epilepsy group were diagnosed with AD and hospitalized younger as the AD group without epilepsy, and their duration of AD was longer. No association between neuropathological diagnosis and group ($\chi2$ (3, n = 64) = 4.626, $p = .170$), and neither between ApoE genotype and group ($\chi2$ (4, n = 64) = 4.433, $p = .274$) were found using Chi-Square Independence Test, although the effect sizes would suggest large or nearly large associations (Cramer's $V = .279$, and Cramer's $V = .295$, respectively). The seizure types were available from six subjects. Four out of the subjects presented with generalized seizures and two with focal seizures. None of the AD-epilepsy patients had experienced a status epilepticus. One of the patients with AD-epilepsy had experienced a traumatic brain injury (TBI) in the past and two were heavy smokers. No abundant alcohol use was reported in the subjects in the AD+EP group. EEG was available for ten of the subjects in the AD+EP group. Seven subjects had a generalized EEG abnormality, one subject with irritation, focal finding and

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discharges, one with irritation and a focal finding and one with a generalized EEG abnormality and a focal finding. The age at time time of first seizure ranged between 62 and 81 years (mean 72.6±6.8 S.E). Epilepsy was diagnosed 2.5±1.2 S.E. years after the diagnosis of AD. The age of starting treatment with antiepileptic medication is known for five subjects, 75±6.9 S.E years (range 66-82 years). Three of the subjects with epilepsy used phenytoin, three carbamazepine and for four subjects this data is not available. One of the subjects did not use any antiepileptic drugs and all subjects used diazepam for seizures.

## Discussion

The present understanding is that patients suffering from AD are at a higher risk for epilepsy than individuals without AD[1,2]. The clinical diagnostic accuracy of AD has improved significantly during the last decades. However, most of the epidemiological studies on these two often interlinked disorders have not included a full post mortem examination of the brain. Therefore, some of the studies lack the verification of the exact cause of clinical dementia. In this clinicopathological study including a systematic neuropathological evaluation we evaluated the characteristics of 64 subjects with neuropathologically verified AD and assessed the subjects especially for concomitant epilepsy. Our main finding is that 17% with neuropathologically verified AD and possible concomitant neurodegenerative pathology had a history of epileptic seizures. Thus, the prevalence of epilepsy is comparable to previous studies[1,2] and was interestingly identical to a previous clinicopathological study including 446 patients with neuropathologically verified AD[10]. It is necessary to point out that the clinical and clinicopathological studies are not directly comparable due to the lack of post mortem examination in many studies revealing the neuropathology causing dementia. Concomitant pathology, i.e. AD/LBD, AD/VaD been shown to be a common finding in elderly subjects with AD[11] and in line with this, concomitant neuropathological were common both in patients with and without epilepsy. In this clinicopathological study we found that the duration of AD was significantly longer in subjects with AD and epilepsy and they were hospitalized at a younger age. In addition, the age at the time of AD diagnosis was significantly lower in the AD and epilepsy group. This may suggest that the AD progresses more rapidly in the subjects with epilepsy. Previously it has been shown that patients with autosomal dominant early-onset AD present with more frequent seizures than patients with sporadic AD[12]. Howerver, in our study the frequency of the ApoE4 allele, which is a well characterized risk factor for earlier onset AD, and the load of β-amyloid as well as well as the other alleles did not differ between statistically between the groups. Frequent seizures may possi-

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bly lead to faster detoriation of the already fragile neuronal networks of the AD subjects. This may lead to a vicious circle accelerating the underlying neurodegenerative process. Thus, the patients require adequate antiepileptic treatment. In this study, we reported that 17% of elderly subjects with neuropathologically verified AD had a history of epilepsy. We have shown that the patients with both AD and epilepsy differ significantly from the subjects with neuropathology restricted to AD and possible concomitant disease processes. More studies on larger post mortem material are warranted in order to more precisely define the characteristics of this group of AD patients as this may eventually affect the current treatment strategies and lead to a slower cognitive decline.

Declarations of interest: none.

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References:


1. Amatniek JC, Hauser WA, DelCastillo-Castaneda C, et al. Incidence and predictors of seizures in patients with Alzheimer's disease. Epilepsia. 2006;47:867–72.
2. Scarmeas N, Honig LS, Choi H, et al. Seizures in Alzheimer disease: who, when, and how common? Arch Neurol. 2009;66:992–7.
3. Cloyd J, Hauser W, Towne A, et al. Epidemiological and medical aspects of epilepsy in the elderly. Epilepsy Res. 2006;68S:S39–48.
4. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 1993;34:453–68.
5. Romanelli MF, Morris JC, Ashkin K, et al. Advanced Alzheimer's disease is a risk factor for late-onset seizures. Arch Neurol. 1990;47:847–50.
6. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34:939–939.
7. Parkkinen L, Soininen H, Alafuzoff I. Regional distribution of alpha-synuclein pathology in unimpaired aging and Alzheimer disease. J Neuropathol Exp Neurol. 2003;62:363–7.
8. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD): Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology. 1991;41:479–479.
9. Tsukamoto K, Watanabe T, Matsushima T, et al. Determination by PCR-RFLP of apo E genotype in a Japanese population. J Lab Clin Med. 1993;121:598–602.
10. Mendez MF, Catanzaro P, Doss RC, et al. Seizures in Alzheimer's Disease: Clinicopathologic Study. J Geriatr Psychiatry Neurol. 1994;7:230–3.
11. Kovacs GG, Alafuzoff I, Al-Sarraj S, et al. Mixed brain pathologies in dementia: The BrainNet Europe consortium experience. Dement Geriatr Cogn Disord. 2008;26:343–50.
12. Zarea A, Charbonnier C, Rovelet-Lecrux A, et al. Seizures in dominantly inherited Alzheimer disease. Neurology. 2016;87:912–9.

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Figure legend

Figure 1. a) Distribution of the neuropathological diagnosis between the groups b) distribution of ApoE genotypes between the groups c) distribution of neuropathological diagnoses and ApoE genotypes. Error bars represent the 95% confidence interval (CI)

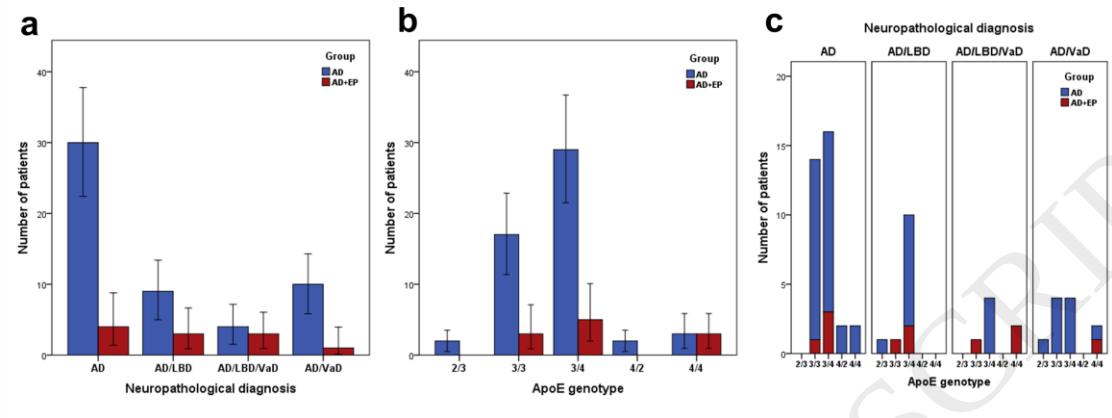


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Table 1.

| | Mean ± SD | | Group comparisons |
|---|---|---|---|
| | **AD[1] + EP[2] (n = 11)** | **AD (n = 53)** | |
| **Male/Female** | 0/11 | 6/47 | |
| **Age at death** | 81.4±8 | 85.3±9 | $t(62) = .1.348$, $p = .182$ |
| **Age at the time of AD[1] diagnosis** | 70.6±7 | 78.3±10 | $t(59) = .2.373$, $p = .021$* |
| **Age at the time of hospitalisation** | 72.6±7 | 79.2±9 | $t(58) = .2.338$, $p = .023$* |
| **Brain weight in grams** | 1013±120 | 1067±148 | $t(61) = .1.147$, $p = .256$ |
| **Duration of AD** | 10.7±5 | 7.1±4 | $t(59) = .-2.496$, $p = .015$* |
| **Neuropathological diagnosis** | | | |
| **AD** | n=4 (36.4%) | n=30 (56.6%) | $\chi^2$ (3, n = 64) = 4.626, |
| **AD+LBD[3]** | n=3 (27.3%) | n=9 (17.0%) | $p = .170$[5], |
| **AD+LBD+VaD[4]** | n=3 (27.3%) | n=4 (7.5%) | Cramer's V = .279 |
| **AD+VaD** | n=1 (9.1%) | n=10 (18.9%) | |
| **ApoE[5] genotypes** | | | |
| **2/3** | 0 (0.0%) | 2 (3.8%) | $\chi^2$ (4, n = 64) = 4.433, |
| **3/3** | 3 (27.3%) | 17 (32.1%) | $p = .274$[5], |
| **3/4** | 5 (45.5%) | 29 (54.7%) | Cramer's V = .295 |
| **4/2** | 0 (0.0%) | 2 (3.8%) | |
| **4/4** | 3 (27.3%) | 3 (5.7%) | |

[1] Alzheimer's disease [2] Epilepsy [3] Dementia with Lewy bodies [4] Vascular dementia
[5] Apolipoprotein E * Group difference significant at .05 α level (Fischer's Exact Test)

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