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Epilepsy in neuropathologically verified Alzheimer's disease

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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 hospitalisation. 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.

1. 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 diseases, 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.

2. 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

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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 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 (Fig. 1).

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.

3. 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 ($F(1,59) = 5.632$, $p = 0.021$), in age at the time of hospitalisation ($F(1,58) = 5.468$, $p = 0.023$), and in duration of AD ($F(1,59) = 6.229$, $p = 0.015$) 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 ($p = 0.182$ and $p = 0.256$, 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 ($\chi 2$ (3, n = 64) = 4.626, $p = 0.170$), and neither between ApoE genotype and group ($\chi 2$ (4, n = 64) = 4.433, $p = 0.274$) were found using Chi-Square Independence Test, although the effect sizes would suggest large or nearly large associations (Cramer's $V = 0.279$, and Cramer's $V = 0.295$, 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 discharges, one with irritation and a focal finding and one with a generalized EEG abnormality and a focal finding. The age at 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.

4. 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

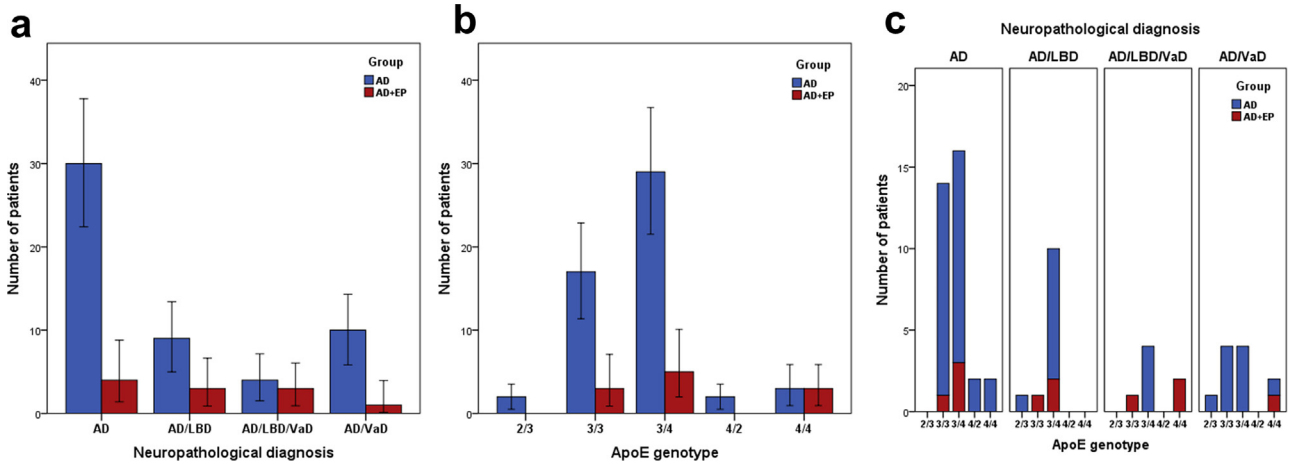

Fig. 1. a) Distribution of the neuropathological diagnosis between the groups b) distribution of ApoE genotypes between the groups c) distribution of neuropathological diagnoses and ApoE genotypes. Error bars represent the 95% confidence interval (CI).