Understanding heterogeneity in Alzheimer's disease:

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2014

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EEG abnormalities in early and late onset Alzheimer's Disease: understanding heterogeneity

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J Neurol Neurosurg Psychiatry 2011;82:67-71

Chapter 2

Abstract

Objective
To compare differences in severity and type of EEG abnormalities between early and late onset Alzheimer's disease (AD) and to assess the influence of APOE genotype on this association, in order to understand the biological differences in AD according to age at onset

Method
Of 460 probable AD patients and 336 patients with subjective complaints, serving as controls, EEG and APOE ε4 genotype were obtained. Subjects were categorised by age into a younger (≤ 65 years) and an older group (> 65 years), based on age at diagnosis. Severity and type of EEG abnormalities were visually assessed. Severity of EEG abnormalities ranged from normal to slightly abnormal to moderately severe. EEG abnormalities were characterized as only focal abnormalities, only diffuse abnormalities or both focal and diffuse abnormalities.

Results
Logistic regression revealed that younger AD patients more often had EEG abnormalities, which were more severe, with a predominance of both focal and diffuse abnormalities. In controls we observed the opposite, as older controls more often had EEG abnormalities than younger controls. Furthermore, APOE ε4 negative AD patients had more severe EEG abnormalities than APOE ε4 positive AD patients, while no such effect was observed in controls. There was no interaction between age at onset and APOE ε4 genotype.

Conclusion
Early onset and APOE ε4 negative AD patients present with more severe EEG abnormalities than late onset and APOE ε4 positive AD patients. These results suggest that in younger patients, AD manifests with more prominent functional brain changes.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia. Although it is typically regarded as a disease of old age, it does occur in younger patients (i.e. before the age of 65 years), commonly referred to as early onset AD. The characteristic clinical presentation of AD in the elderly consists of progressive memory impairment, followed by global cognitive decline. Early onset AD often presents in a different way compared to AD with late onset. Early onset AD patients more often show focal impairments like aphasia and apraxia,[1-4] and a more rapid cognitive decline.[5,6] APOE-ε4 genotype is associated with age at onset.[7] Moreover, it has been suggested that APOE ε4 carriers present with more severe memory impairment, while conversely non-carriers present with more pronounced impairment in other cognitive domains.[8,9] These differences in presentation suggest the existence of heterogeneity within the spectrum of AD.
EEG can be used to distinguish AD patients and healthy controls, with a positive predictive value between 75-80% in visual as well as quantitative analysis.[10] Hallmarks of EEG abnormalities in AD are an increase in diffuse slow activity and a reduction in alpha and beta activities.[11] Studies on EEG in early onset AD are sparse. In a small group of early onset AD patients an increase of power in the slow frequency bands and a decrease of power in the fast frequency bands was found, compared to age-matched controls.[12] However, no comparison was made between early onset and late onset AD. In another study, correlations were found between several EEG parameters and age at onset of AD. A more 'abnormal' EEG occurred in patients with a younger age of onset.[13]

In the present study we aimed to compare differences in severity and type of EEG abnormalities between early onset and late onset AD by visual EEG analysis in a large population of AD patients. A group of controls was included for comparison. Furthermore we assessed how APOE genotype influenced this association. We hypothesized that patients with early onset AD have more often and more severe EEG abnormalities compared to patients with late onset AD.

Methods

Subjects

We included 460 probable AD patients and 336 patients with subjective complaints that had been referred to the memory clinic of the Alzheimer center of the VU university medical center, Amsterdam, the Netherlands between March 2001 and June 2009. Standardised dementia screening included a history and, when available, an informant based history, a standard neurological examination, a cognitive examination including Mini Mental State Examination (MMSE), electroencephalography (EEG), Magnetic Resonance Imaging (MRI) of the brain, neuropsychological evaluation and laboratory tests. Patients were diagnosed with probable AD according to the NINCDS-ADRDA criteria14 during a multidisciplinary consensus meeting. When the test results of all examinations, including neuropsychological investigations, were normal, patients were considered to have subjective complaints (i.e., patients did not fulfil criteria for MCI). To rule out the influence of past medical history on EEG characteristics, we excluded 54 patients, with a past medical history of epilepsy, serious head trauma, ischemic stroke, haemorrhagic stroke, subarachnoid haemorrhage, multiple sclerosis, meningitis, encephalitis or intracranial space occupying lesions. Patients were categorised in younger (65 years or younger; n= 154) and older (older than 65 years; n=280) category, based on age at diagnosis. Controls were categorised in a younger (n=211) and an older (n=97) age group, based on the same age criterion. The study has been approved by the ethical review board of the VU University Medical Center. All patients gave written informed consent to use their clinical data for research purposes.

EEG recording

All EEGs were recorded using the Nihon Kohden digital EEG apparatus (EEG 2100), and since September 2003, OSG digital equipment (Brainlab®; OSG b.v., Rumst, Belgium) at the positions of the 10-20 system: Fp2, Fp1, F8 F7, F4, F3, A2, A1, T4, T3, C4, C3, T6, T5, P4, P3, O2, O1, Fz, Cz, Pz. Sample frequency was 200 Hz for the Nihon Kohden system and 500 Hz for the OSG Brainlab system. Electrode impedance was below 5kW. Initial filter settings were: time constant 1s; low pass filter, 70 Hz. Patients were seated in a slightly reclined chair in a

sound attenuated room. Patients sat mainly with eyes closed, EEG technicians were alert on keeping patients awake by sound stimuli.

Visual EEG assessment

Bod clinical neurophysiologists assessed all EEG recordings, without knowledge of clinical information. Type of EEG abnormalities consisted of two dichotomous variables: focal abnormalities and diffuse abnormalities.15Presence of focal abnormalities was defined as (transients of) slow or sharp wave activity in 1 or more EEG leads, excluding benign temporal theta of the elderly (BTTE).16 Presence of diffuse abnormalities was defined as a dominant frequency of rhythmic background activity below 8 Hz, diffuse slow-wave activity or diminished reactivity of the rhythmic background activity to the opening of the eyes. These two variables were combined in a third 4-level variable: (i) no abnormalities, (ii) only focal abnormalities, (iii) only diffuse abnormalities and (iv) both focal and diffuse abnormalities. In addition, severity of EEG abnormalities was rated using a 4-point scale, ranging from no abnormalities to severe abnormalities. Due to very small group size for severe abnormalities (n=4), the groups moderately severe and severe abnormality were merged, resulting in 3 levels in the severity variable: none, mild, moderate to severe abnormalities. In previous reports by our study group kappa-values for inter observer agreement between .60 and .87 have been reported.15

APOE genotyping

APOE genotyping was performed after DNA isolation from 10 ml EDTA blood, with the Light Cycler APOE mutation detection method (Roche Diagnostics GmbH, Mannheim, Germany). APOE-ε4-carrier ship was dichotomized in negative or positive, with positive containing both homozygous and heterozygous APOE-ε4 carriers.

Statistics

SPSS 15.0 for Windows was used for statistical analyses. Differences between groups for baseline characteristics were investigated with t-tests and c2-tests where appropriate. Differences in prevalence of EEG abnormalities between groups were investigated by c2-tests. Subsequently, to adjust for sex, use of psychotropic medication and to assess the combined effect of age and APOE genotype on EEG abnormalities, logistic regression analyses were performed. Presence of EEG abnormalities, dichotomized as no abnormalities versus any

abnormalities, was used as dependent variable. In model 1, the effects of both age and APOE genotype were assessed unadjusted in separate models. In model 2 we adjusted for sex and use of psychotropic mediation. In model 3 both age and APOE genotype, adjusted for sex and use of psychotropic medication, were entered simultaneously. Interaction between age group and APOE genotype was assessed. For age, older age group was used as reference group and for APOE the positive genotype was used as reference group. Odds Ratio (OR) and 95% confidence intervals are reported

Results

Baseline characteristics are presented for patients and controls according to age (table 1). The mean age in the AD group was higher than in the control group, for both the younger and the older patients. AD patients were more often APOE 4 positive than controls. In the group of AD patients there was no difference in sex or APOE ε4-carriership according to age. The younger AD group had a lower MMSE-score than the older AD group. In controls there was no difference in sex, MMSE-score or APOE ε4-carriership according to age.

Table 2 shows the prevalence of type and severity of EEG abnormalities. Younger AD patients more often showed EEG abnormalities than older ones ($p < .05$), especially a combination of focal and diffuse abnormalities. Furthermore, the observed EEG abnormalities were more severe in younger patients than in older patients ($p < .05$). Examples of characteristic EEGs of both a younger AD patient and an older AD patient are shown in **figure 1**. In controls we found the opposite pattern: EEG abnormalities were found more often in older controls than in younger controls ($p < .01$), although there was no significant difference in severity of abnormalities ($p = .54$).

Figure 2 shows the association between EEG abnormalities and APOE ε4 genotype. We observed that APOE ε4 negative AD patients had more severe EEG abnormalities than APOE e4 positive patients ($p <. 05$); we found no effect of APOE ε4 genotype on type of EEG abnormalities. In controls there was no effect of APOE ε4 genotype on type or severity of EEG abnormalities.

Subsequently, we used logistic regression to adjust for sex and use of psychotropic medication (see table 3). EEG abnormalities were dichotomized as no abnormalities or any severity of abnormalities. Younger AD patients had an increased risk of EEG abnormalities, compared to older patients (OR 1.7, 95% CI 1.1-2.8). APOE ε4 negative AD patients had a modestly, though non-significantly, increased risk of EEG abnormalities, as opposed to APOE ε4 positive patients (OR 1.5, 95% CI 0.9-2.4). When we entered both age and APOE ε4 genotype in one model, the effects remained of comparable strength. There was no interaction between APOE ε4 genotype and age at onset of AD (p = .70).

Discussion

We found that younger AD patients more often had a combination of focal and diffuse EEG abnormalities than older AD patients. They also had more severe EEG abnormalities than older AD patients. In controls, the opposite effect was found: more often and more severe EEG abnormalities occurred in older controls. In APOE ε4 negative AD patients severe EEG abnormalities occurred more often than in APOE ε4 positive patients. This effect was independent of the effect of age.
Our results are in line with the few earlier studies that reported more severe EEG abnormalities in early onset AD. In a quantitative EEG study on patients with early onset AD opposed to controls, early onset AD patients showed an increase of power in the slow frequency bands.12 In a study comparing early onset AD patients with late onset AD patients, significant correlations were found between age at onset and relative power in different frequency bands.13 We extend on these former studies by including a large sample of AD patients and controls, showing that the effect of age on EEG has opposite directions in these two groups.

Earlier research on the difference between early onset and late onset AD showed evidence of heterogeneity in other modalities as well: early onset AD patients show more global atrophy with a faster atrophy rate,17 disproportionate precuneus atrophy18and a more severe glucose hypometabolism in parietal, frontal and subcortical areas.19 These findings suggest the involvement of different regions, and perhaps of different neuronal networks. Our findings

show that brain function is differentially affected in AD patients with early and late onset. Further study is needed to take regional changes in brain function into account.

In addition to the effect of age, we also explored the influence of APOE ε4 genotype on EEG abnormalities. Since it has been shown before that the effect of age at onset may be modified by APOE genotype,[7,20,21] we examined if there was an interaction between age at onset and APOE ε4 genotype on the prevalence of EEG abnormalities. This was not the case, but we did find a main effect of APOE ε4 genotype, with APOE ε4 negative AD patients having more prominent EEG abnormalities than APOE ε4 positive patients. This is in contrast to most earlier studies, which found more EEG slowing in APOE ε4 positive patients.[20,22,23] Studies on functional connectivity report conflicting results: one study found a higher connectivity in APOE ε4 positive patients,[24] whereas another study found a reduced connectivity in APOE ε4 positive patients.[25] In both studies no slowing in quantitative EEG analysis for APOE ε4 positive patients was found. We are not sure what the reason is of our finding more prominent EEG abnormalities in APOE ε4 negative patients, but we feel that these findings are in line with former observations of APOE ε4 negative AD patients more often showing a more aggressive clinical course, especially when they are young.[5,17]

Strengths of this study are the large cohort size including AD patients as well as controls with a wide age range, and the use of visual analysis, which together make the findings in our study quite robust. Visual analysis is a relatively easy and fast way of analysing EEG's and, for clinical purposes, the visual assessment of EEG is equal to quantitative analysis, with a high sensitivity for moderate-to-severe dementia.[26] A former study demonstrated that visual EEG analysis can be used to differentiate between different diagnoses in a memory clinic population.[15] Another tool for visual EEG analysis, the Grand Total of EEG (GTE) score, has proven to be useful in the diagnostic evaluation of AD[27] and in differentiating between DLB and AD with good sensitivity and specificity.[28] In the present study, we show that visual analysis can also differentiate subgroups within the spectrum of AD.

The results of this study give further evidence for the existence of biological differences between early onset and late onset AD. We demonstrated that early onset AD patients show more EEG abnormalities than late onset AD patients.

This implies that early onset AD patients behave differently than late onset patients not only on a structural, behavioural and cognitive level, but also on the level of brain function. An underlying structural and functional difference in different patient groups within AD is of great clinical importance, since it can help making an early diagnosis, it can influence the kind of treatment needed and it might imply a different prognosis.

Acknowledgement

The Alzheimer Center VUmc is supported by Alzheimer Nederland and Stichting VUmc fonds. The clinical database structure was developed with funding from Stichting Dioraphte.

Competing interests

H. de Waal, M.A. Blankenstein, Y.A.L. Pijnenburg, P. Scheltens and W.M. van der Flier report no competing interests. C.J. Stam is member of the Journal of Neurology, Neurosurgery & Psychiatry Editorial Board.

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Table 1. Baseline characteristics of memory clinic population

	Baseline characteristics			
	AD		Control	
	younger	older	younger	older
n	154	280	211	97
Age	59 (5)$_a$	75 (5)$_b$	55 (7)	72 (4)
Sex, female	84 (55%)	138 (49%)	89 (42%)	49 (51%)
MMSE-score	20 (6)$_c$	21 (5)	28 (2)	28 (1)
APOE,e4 positive	109 (71%)$_a$	186 (66%)$_b$	70 (33%)	40 (41%)

Values are mean (SD) or n (%). $_a$early onset AD group versus younger controls: $p < .05$. $_b$late onset AD group compared to older controls: $P<.05$. $_c$early onset AD versus late onset AD: $p < .05$.

Table 3. Influence of age at onset of AD and APOE ε4 genotype on EEG abnormalities.

	Model 1	Model 2	Model 3
Age (early/late)	1.8 (1.1-2.8)*	1.8 (1.1-2.9)*	1.8 (1.1-2.9)*
APOE genotype (positive/negative)	1.5 (0.9-2.5)	1.6 (1.0-2.6)	1.7 (1.0-2.7)*

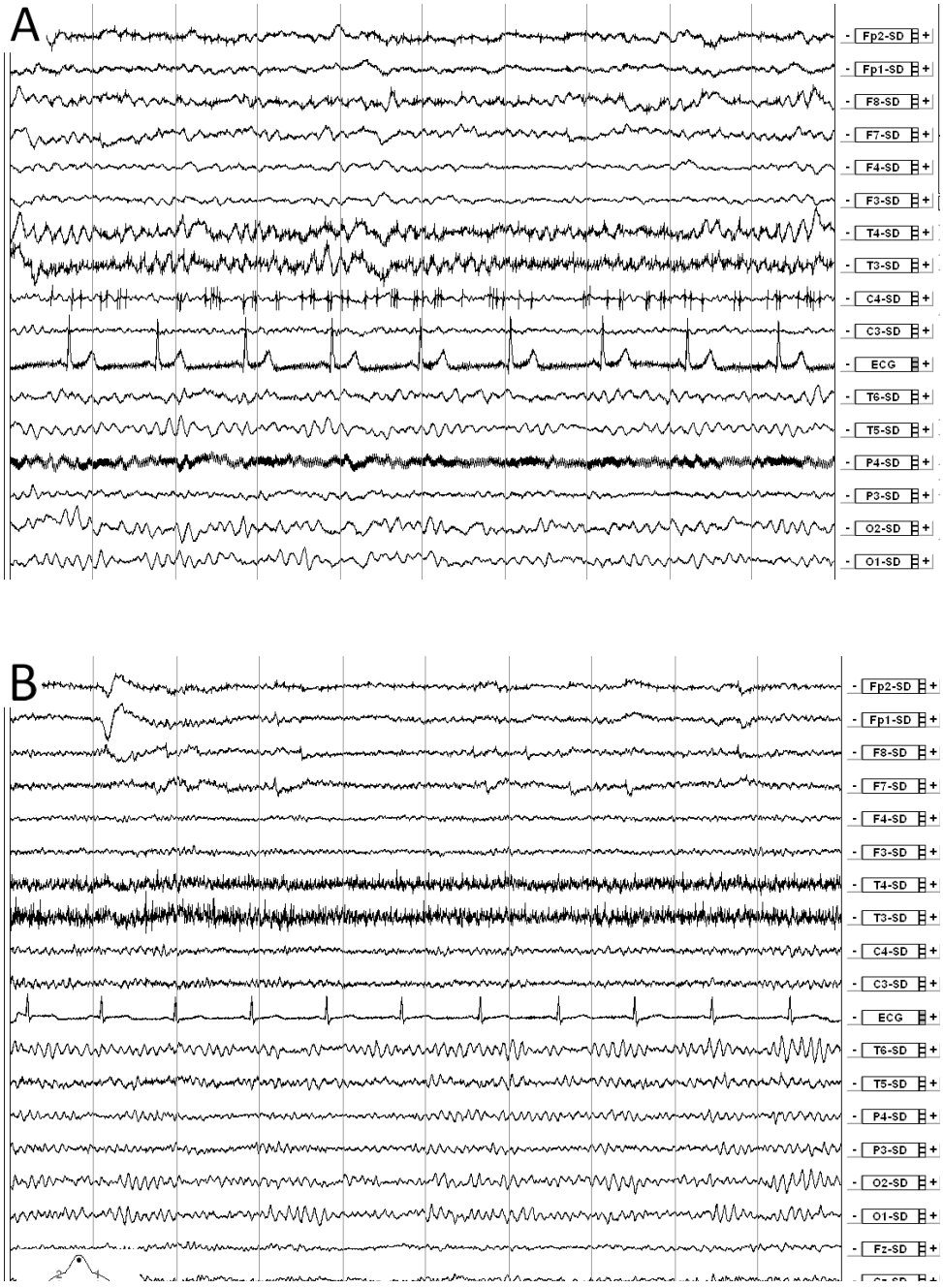
Data are presented as Odds Ratio (95% Confidence Interval). For age: 'late' is reference category. For APOE ε4 genotype: 'positive' is reference category Model 1: univariate; Model 2: sex and medication as covariates; Model 3: both age and APOE genotype are entered in the model.

Table 2. Prevalence of type and severity of EEG abnormalities in AD patients and controls.

	AD			Control		
	younger (154)	Older (280)	p-value	Younger (228)	Older (105)	p-value
Type of EEG abnormalities			.027*			.003*
Normal	29 (19%)	81 (29%)		134 (64%)	56 (58%)	
Only focal abnormalities	38 (24%)	80 (29%)		73 (35%)	31 (32%)	
Only diffuse abnormalities	21 (14%)	34 (12%)		0 (0%)	5 (5%)	
Focal and diffuse abnormalities	66 (43%)	85 (30%)		4 (2%)	5 5%)	
Severity of EEG abnormalities			.015*			.539
Normal	29 (19%)	81 (29%)		134 (64%)	56 (58%)	
Slightly abnormal	69 (45%)	129 (46%)		70 (33%)	36 (37%)	
(Moderately) severe	56 (36%)	70 (25%)		7 (3%)	5 (5%)	

Statistics are performed using Chi-square test, difference in prevalence according to age.

Figure 1


A
- Fp2-SD +
- Fp1-SD +
- F8-SD +
- F7-SD +
- F4-SD +
- F3-SD +
- T4-SD +
- T3-SD +
- C4-SD +
- C3-SD +
- ECG +
- T6-SD +
- T5-SD +
- P4-SD +
- P3-SD +
- O2-SD +
- O1-SD +
B
- Fp2-SD +
- Fp1-SD +
- F8-SD +
- F7-SD +
- F4-SD +
- F3-SD +
- T4-SD +
- T3-SD +
- C4-SD +
- C3-SD +
- ECG +
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- O1-SD +
- Fz-SD +

Figure 2

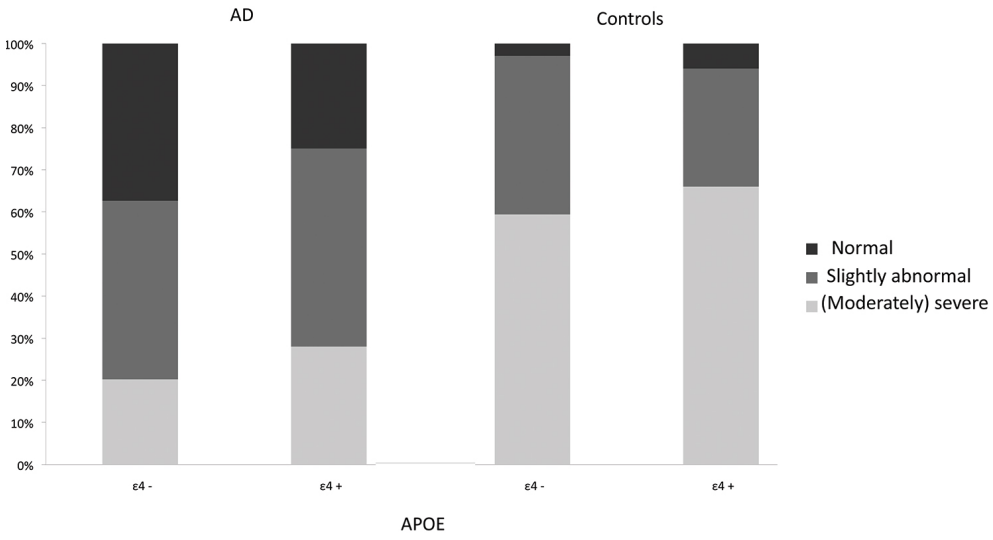

Figure 1 (p. 38)
A: example of characteristic EEG of early onset AD patient. Patient is a 57 year old male, MMSE score 29 B: example of characteristic EEG of late onset AD patient. Patient is a 79 year old female, MMSE score 27.

Figure 2 (p. 39)
Bar graph representing the association between APOE genotype and severity of EEG abnormalities. In AD, APOE ε4 negative patients had more severe EEG abnormalities than APOE ε4 positive patients ($p < .05$). In controls there was no effect of APOE ε4 genotype on severity of EEG abnormalities.