Quantitative Spectral Electroencephalography in Predicting Survival in Patients With Early Alzheimer Disease

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Objective: To determine whether measures of quantitative spectral electroencephalography (EEG) can predict survival in patients with early Alzheimer disease.

Design: Prospective cohort study; median duration of follow-up was 4.4 years in survivors and 2.6 years in non-survivors. Cox proportional hazards models, with adjustment for age and sex were used to estimate relationships between EEG measures and survival. Log relative percentage values of EEG bands were used as predictors.

Setting: Outpatient university memory clinic.

Participants: One hundred one consecutively referred patients with early probable Alzheimer disease according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association criteria were studied with EEG at the time of diagnosis. The mean age of the patients was 79.2 years, which was higher than in previous EEG studies.

Main Outcome Measure: Mortality.

Results: Fifty-one patients (50.5%) died during follow-up, with a median survival time in all patients of 4.1 years. The following EEG variables were significantly associated with increased risk of mortality: from parieto-occipital leads, higher theta (hazard ratio, 2.05; 95% confidence interval, 1.15-3.66; P < .05), lower alpha (hazard ratio, 0.43; 95% confidence interval, 0.25-0.76; P < .01), and lower beta (hazard ratio, 0.38; 95% confidence interval, 0.22-0.68; P < .001) activity; and from frontocentral leads, higher theta activity (hazard ratio, 2.07; 95% confidence interval, 1.17-3.66; P < .05). Stepwise Cox regression analysis showed that loss of parieto-occipital beta (P < .01) and alpha (P < .05) power were independent and significant predictors of mortality. Both beta (12.6-35.4 Hz) and alpha (7.5-12.5 Hz) activity remained significantly associated with mortality after adjustment for education, dementia severity, symptom duration, level of cognitive function, presence of extrapyramidal symptoms or hallucinations, presence of vascular risk factors, and presence of leukoaraiosis or local cortical atrophy.

Conclusions: Decreases of beta and alpha activity on quantitative spectral EEG are independent predictors of mortality in patients with early Alzheimer disease. In the clinical context, the use of EEG technology for prediction of survival in individual patients remains to be determined.

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Electroencephalogram (EEG) abnormalities in Alzheimer disease (AD) include increase of theta and delta activity and reduction of beta power.1-5 The changes in theta activity may occur early in the disease, whereas increase of delta is reported in the late stages.2 Follow-up studies show that slowing on spectral EEG at baseline is associated with more severe cognitive and functional decline in patients with AD.6-8 Although prediction of survival in patients with AD is important for family and caregivers and for planning of patient care, there are few follow-up studies on the predictive ability of EEG for survival in AD.3,8-10 The results have been inconsistent, with some studies reporting an association of EEG variables at baseline and survival3,8-10 while in a more recent report this association was not statistically significant.8 Moreover, study populations included selected hospitalized patients10 and small numbers of patients,3,9 and the mean follow-up time was not more than 3 years.3,8-10

Clinical features, including extrapyramidal symptoms, and neuroimaging characteristics, such as presence of periventricular white matter lesions or cortical atrophy, are reportedly associated with EEG abnormalities.11-13 It is possible that these factors explain the relationship between an abnormal EEG at baseline and the presumed risk of increased mortality. It is therefore necessary to examine the re-
PATIENTS AND METHODS

PATIENTS

Patients met criteria for probable AD according to National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer’s Disease and Related Disorders Association criteria and were participants in a prospective study of 200 consecutive first referrals to the outpatient memory clinic of the Academic Medical Center, Amsterdam, the Netherlands. Inclusion criteria were referral for suspected dementia, age 65 years and older, and presence of an informant involved in the care of the patient; patients who were previously investigated for dementia were excluded. At baseline, all subjects were examined with the Netherlands version of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX-N), computed tomography (CT), EEG, and laboratory screening. Of the 200 patients initially referred, 105 were diagnosed as having probable AD, but 4 EEGs were missing because of technical reasons, leaving 101 patients in the study (43 men and 58 women). All patients and legally authorized representatives gave informed consent to participate in this study. Survival data were obtained from general practitioners and were available for all patients. Presence of extrapyramidal signs was defined as having at least 1 of the following signs at neurological examination: tremor, rigidity, bradykinesia, abnormal postural reflexes, or a characteristic parkinsonian gait. Clinical indicators used to define presence of 1 or more vascular risk factors included history of diabetes mellitus, hypertension, myocardial infarction, transient ischemic attacks, or stroke. Presence of delusions or hallucinations was determined by questioning the caregiver according to the standardized interview with the CAMDEX-N.

Ten patients used benzodiazepines; no other centrally active medication was used.

EEG METHODS

As described previously, EEG recordings were performed at baseline with the use of an on-line 20-channel EEG system, with the international 10/20 system and silver–silver chloride electrodes. The impedance of the electrodes was always lower than 5 kΩ. The high-frequency cutoff was 35 Hz (~3 dB, 12 dB/octave), and the time constant was 0.3 seconds. The EEG was recorded under vigilance control with the patient’s eyes closed under resting conditions. With visual inspection to rule out segments with artifacts, such as electromyogram or electrocardiogram activity or eye movement, only artifact-free periods were used for quantitative analysis. Computerized spectral analysis was performed by means of fast Fourier analysis after sampling at a rate of 70 Hz on 6 bipolar frontocentral and parieto-occipital derivations: F3 to C3, T5 to O1, F4 to C4, T6 to O2, P3 to O1, and P4 to O2. After fast Fourier analysis was performed on an epoch of 3.36 seconds with a bin width of 0.298 Hz, the power spectrum of this epoch was calculated and an average power spectrum was computed as the mean of 30 successive epochs. Subsequently, this average power spectrum was then filtered with a 3-point triangular symmetrical filter. This filter did not influence the frequency value of the peak. Leakage of power to other frequencies caused by the triangular window did not significantly influence the power within a spectral band, as the spectral bands consisted of at least 12 points and leakage was restricted to only 1 point. The frequency bands were set as follows: delta, 0.3 to 3.5 Hz; theta, 3.6 to 7.4 Hz; alpha, 7.5 to 12.5; and beta, 12.6 to 35.4 Hz. Since absolute values may suffer from large variability, relative values (percentage) were calculated by dividing the absolute power in each frequency band by the total power of the whole spectrum in all 4 bands. Then, a logarithmic transformation was performed to compensate for data skewness with the formula log(x/(1−x)), where x refers to the relative value.

CT STUDIES

Computed tomography was performed with a scanner (Somatom Plus or HiQ; Bruker AXS, Inc, Erlangen, Germany) in all patients. Consecutive slices were obtained parallel to the canthomeatal line, with a thickness of 5 mm up to and

RESULTS

Some subject characteristics are presented in Table 1. Relative power EEG values in percentage of delta, theta, alpha, and beta band, respectively, are shown in Table 2. Means of combined right and left EEG variables were calculated for frontocentral and parieto-occipital regions, since no differences between homologous left and right measurements were observed (Table 2). Fifty-one patients (50.5%) died during the follow-up period, with a median (± SD) survival time of 4.1 ± 0.2 years. The following variables were statistically significantly associated with increased risk of mortality: higher age (per 5-year increase, hazard ratio [(HR)], 1.26; 95% CI, 1.01–1.57; P < .05), male sex (HR, 1.92; 95% CI, 1.12–3.23; P < .05), lower score on the cognitive test from the CAMDEX-N (HR per 10-point decrease, 1.43; 95% CI, 1.19–1.69; P < .001), lower score on the Mini–Mental State Examination (HR per 5-point decrease, 1.47; 95% CI, 1.19–1.82; P < .001), and more severe dementia (HR, 2.18; 95% CI, 1.19–3.99; P < .05), but not education (HR, 1.07; 95% CI, 0.89–1.28; P = .88) and symptom duration (HR, 1.0; 95% CI, 0.99–1.01; P = .54).

Higher parieto-occipital (P < .05) and frontocentral (P < .05) theta activity, and lower parieto-occipital
alpha (P < .01) and parieto-occipital beta (P < .001) activity were statistically significantly associated with increased risk of mortality, adjusted for age and sex (Table 3). Stepwise Cox regression analysis showed that parieto-occipital beta activity was the strongest predictor of survival in AD (P < .01), while parieto-occipital alpha power was retained in the model with additional predictive ability (P < .05). Thus, both parieto-occipital beta and alpha power were used for further analyses. The relationships between parieto-occipital beta and alpha activity and survival remained statistically significant after adjustment for all possible confounders examined in this study and after exclusion of subjects with a history of transient ischemic attacks or stroke. Since our patients had relatively high delta power in parieto-occipital leads and delta power may increase with advancing age,1 the relatively high age of our study population might suggest that delta is a marker of dementia severity, independent of the CAMDEX-N dementia severity marker used in our study. However, delta power was statistically significantly associated with general level of cognitive function, both the cognitive test of the CAMDEX-N (P < .01) and the Mini–Mental State Examination (P < .01), as well as dementia severity (P < .05). Further, the association between beta and alpha power and survival was not changed with the addition of parieto-occipital delta power to the Cox regression model as correction factor, with the use of multiple linear regression analysis with adjustment for age and sex. The possibility that we included patients with Lewy body dementia was considered, since this subgroup of patients appears to have more abnormal EEGs than patients with only AD.25 However, no patient in our study satisfied clinical criteria for Lewy body dementia.29 Further, there were no significant differences in alpha (P > .50) or beta (P > .80) power between groups with or without extrapyramidal symptoms, or in alpha (P > .30) or beta (P > .20) power between those with and without delusions or hallucinations, by means of multiple linear regression analysis, with adjustment for age and sex. After a mean of 5.4 years of follow-up, Kaplan-Meier survival curves for groups dichotomized according to the me-
median (−1.14; range, −1.85 to −0.24) log relative percentage beta activity (Figure 1) showed that 59% of the patients with high beta power were alive (median survival time, at least 5.4 years), while 14% of the patients with low beta power were alive (median survival time, 3.2 years). Log rank test for comparison between patients with high vs low beta activity was statistically significant (P < .001). Kaplan-Meier survival curves are also shown for log relative percentage alpha activity in Figure 2, dichotomized according to the median of the distribution. Similar results were obtained when patients using benzodiazepines were excluded (n = 10). Proportionality assumptions of the hazard were met for all EEG variables.

We studied the relationship between EEG at the time of diagnosis and survival in consecutively referred patients with early AD. Low parieto-occipital beta power was the strongest predictor of mortality, while decrease in alpha power also independently contributed to this mortality risk, although to a lesser extent. The predictive power of the EEG for survival was not explained by differences in demographic, clinical, or CT features. Also, the higher percentage delta power in our patients as compared with that in some previous studies is probably related to the greater age of our study population than in these previous studies, since in healthy older subjects delta activity may increase with age.

Indeed, delta activity appeared not to be a marker of severity, independent of the CAMDEX-N dementia severity marker used. In this study, we extended our earlier observations that, from all EEG bands, parieto-occipital beta values were the strongest predictor of cognitive and functional decline in patients with probable AD. This prognostic value was further specified by the observation that low values of beta on EEG were related to rapidly progressive decline.

From a methodological viewpoint, our EEG study on survival in AD differs from previous studies in several aspects, including choice of study population, length of follow-up, inclusion of possible confounders, and approach for statistical analysis. In contrast to some reports, we studied consecutively referred patients for evaluation of memory complaints or (suspected) dementia, and these patients were part of a prospective follow-up study. None of our patients satisfied any of currently used clinical criteria for dementia with Lewy bodies, and alpha and beta power in our study were not different when compared in patients with and without extrapyramidal symptoms, or in those with and without delusions or hallucinations. Electroencephalographic studies in selected groups of patients with AD may limit the external validity to clinical practice. Further, in our study 51.5% of the patients died during follow-up, while in some previous studies these percentages varied from 12.5% to 27.4%. The shorter follow-up in these previous studies may limit the statistical power and may there-

### Table 1. Characteristics of 101 Patients With Alzheimer Disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding</th>
</tr>
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<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
</tr>
<tr>
<td>Age, y (mean ± SD)</td>
<td>79.2 ± 6.3</td>
</tr>
<tr>
<td>Sex, % M/F</td>
<td>42.8 ± 7.2</td>
</tr>
<tr>
<td>Education† (mean ± SD)</td>
<td>3.2 ± 1.5</td>
</tr>
<tr>
<td>Duration of follow-up, mo (mean ± SD)</td>
<td>41.0 ± 16.1</td>
</tr>
<tr>
<td>All patients</td>
<td>52.9 ± 6.3</td>
</tr>
<tr>
<td>Survivors</td>
<td>31.1 ± 51.1</td>
</tr>
<tr>
<td><strong>Medical history, %</strong></td>
<td></td>
</tr>
<tr>
<td>History of TIAs</td>
<td>6.9</td>
</tr>
<tr>
<td>History of stroke</td>
<td>5.0</td>
</tr>
<tr>
<td>Presence of delusions or hallucinations</td>
<td>21.8</td>
</tr>
<tr>
<td>Presence of vascular risk factors</td>
<td>34.6</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
</tr>
<tr>
<td>Symptom duration, y (mean ± SD)</td>
<td>3.0 ± 2.8</td>
</tr>
<tr>
<td>CAMCOG baseline (mean ± SD)</td>
<td>62.4 ± 16.4</td>
</tr>
<tr>
<td>CAMCOG decline per year (mean ± SD)</td>
<td>9.5 ± 8.1</td>
</tr>
<tr>
<td>MMSE baseline (mean ± SD)</td>
<td>17.9 ± 5.6</td>
</tr>
<tr>
<td>MMSE decline per year (mean ± SD)</td>
<td>3.6 ± 3.3</td>
</tr>
<tr>
<td>Dementia severity, %‡</td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>7.9</td>
</tr>
<tr>
<td>Mild</td>
<td>79.2</td>
</tr>
<tr>
<td>Moderate</td>
<td>12.9</td>
</tr>
<tr>
<td>Presence of extrapyramidal signs, %</td>
<td>25.7</td>
</tr>
<tr>
<td><strong>Computed tomographic findings, %</strong></td>
<td></td>
</tr>
<tr>
<td>Presence of leukoaraiosis</td>
<td>30.7</td>
</tr>
<tr>
<td>Presence of right temporoparietal cortical atrophy</td>
<td>70.3</td>
</tr>
<tr>
<td>Presence of left temporoparietal cortical atrophy</td>
<td>69.3</td>
</tr>
<tr>
<td>Cortical infarctions, silent</td>
<td>4.0</td>
</tr>
<tr>
<td>Cortical infarctions, nonsilent</td>
<td>2.0</td>
</tr>
<tr>
<td>Subcortical infarctions, silent</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* TIA indicates transient ischemic attack; CAMCOG, cognitive test from the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) and MMSE, Mini–Mental State Examination.

† Attained level of education, classified on a 7-point scale that ranges from 1 (primary school) to 7 (university) in accordance with the International Standard Classification of Education (Unesco, Paris, France, 1976).

‡ Severity according to CAMDEX criteria.

### Table 2. Quantitative Spectral Electroencephalogram (EEG) Relative Power Values of 101 Patients With Probable Alzheimer Disease

<table>
<thead>
<tr>
<th>Quantitative Spectral EEG Bands*</th>
<th>Delta</th>
<th>Theta</th>
<th>Alpha</th>
<th>Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fronto-central left</td>
<td>49.4 ± 17.7</td>
<td>18.4 ± 10.0</td>
<td>18.1 ± 11.7</td>
<td>14.3 ± 9.8</td>
</tr>
<tr>
<td>Fronto-central right</td>
<td>50.9 ± 17.4</td>
<td>17.7 ± 9.5</td>
<td>17.1 ± 10.7</td>
<td>14.4 ± 9.4</td>
</tr>
<tr>
<td>Parieto-occipital left</td>
<td>41.9 ± 16.9</td>
<td>21.6 ± 11.3</td>
<td>27.7 ± 17.6</td>
<td>8.8 ± 7.0</td>
</tr>
<tr>
<td>Parieto-occipital right</td>
<td>40.5 ± 17.3</td>
<td>20.8 ± 10.7</td>
<td>29.4 ± 18.6</td>
<td>9.3 ± 7.2</td>
</tr>
</tbody>
</table>

* Frontocentral was defined as values of leads F3 to C3 (left) and F4 to C4 (right); parieto-occipital, as the average values of leads T5 to O1 and P3 to O1 (left), and of T6 to O2 and P4 to O2 (right). Relative values are defined as absolute value in 1 band/[(delta + theta + alpha + beta), expressed as mean ± SD percentages. The frequency bands were set as follows: delta, 0.3 to 3.5 Hz; theta, 3.6 to 7.4 Hz; alpha, 7.5 to 12.5 Hz; and beta, 12.6 to 35.4 Hz.
fore explain differences in study results. In the study by Kaszniak et al,\textsuperscript{10} 45.7% of the patients died, but these were hospitalized patients with dementia. Not all previous reports use analysis of separate EEG bands,\textsuperscript{8,10} while the notion that these bands have different regional correlates in the human brain\textsuperscript{31,32} suggests the necessity of separate EEG band analysis. Our approach to use a wide selection of clinical and CT variables to identify factors, rather than the EEG alone, that also may account for the observed relationship between EEG and survival was not used in other studies.\textsuperscript{3,8-10} Furthermore, we extended our analyses by identifying a subset of independent predictive EEG bands.

The predictive ability of the EEG for survival in patients with AD was noted by some authors,\textsuperscript{3,9} but not by others.\textsuperscript{8} Our results are in agreement with an earlier study by Kaszniak et al.\textsuperscript{10} They examined hospitalized patients, probably more severely demented than patients in our population, with a follow-up period of 1 year and reported that 79% of survivors had either normal EEGs or mild diffuse slowing, contrasting with 13% of the deceased patients with similar EEG findings.\textsuperscript{10} Interestingly, they found no differences between survivors and nonsurvivors in baseline demographic and severity of disease characteristics, or in degree of cerebral atrophy on CT. Our results are further supported by 2 other studies reporting that increase of slow activity on EEG is associated with increased risk of mortality.\textsuperscript{3,9} In contrast to our observations, Lopez et al\textsuperscript{8} found that mean frequency as pooled score from parasagittal derivations was not associated with survival in patients with AD. In this study, however, the HR for increased risk of mortality was in the expected direction. Since 27.4% of their patients died, compared with 50.5% in our study, with similar total patient numbers in both studies, their limited statistical power may render their study sensitive to a type II error. Indeed, age and sex were not significant predictors in the study by Lopez et al, whereas these are well-established predictors of survival.\textsuperscript{3,10}

Beta and alpha activity were recognized as independent predictors of survival in our study. These results suggest that beta and alpha activity have pathophysiological correlates in the brains of patients with AD and that these correlates are different for both EEG bands. Preclinical and clinical studies show that several brain structures intimately involved in the pathophysiology of AD are linked to beta activity, including the hippocampus,\textsuperscript{37} the cholinergic nucleus basalis,\textsuperscript{38} and layer II of the entorhinal cortex.\textsuperscript{39} Even in patients with very mild AD, there is a marked loss of layer II entorhinal cortex neurons,\textsuperscript{40} and synaptic cell loss in the hippocampal formation is an early phenomenon in AD.\textsuperscript{41} The observation by Williamson et al\textsuperscript{42} that normal elderly subjects with cognitive decline had a marked reduction in beta activity, contrasting with 13% of the deceased patients with similar EEG findings,\textsuperscript{10} is intriguing in this context. This observation might have resulted from the incorporation of subjects with unrecognized AD in the sample. Reduction of beta activity in
patients with early AD may thus reflect very early neuropathological changes. Further, the predictive ability of decreased beta activity for survival in AD does not simply reflect dementia severity, cortical atrophy, or leukoaraisis, as suggested by our findings. In analogy with Parkinson disease, where only substantial neuronal loss in the substantia nigra results in clinical impairment, a certain amount of neurons in hippocampus and entorhinal cortex may need to degenerate for demonstrable dementia symptoms to be present. The additional predictive ability for survival of decreased alpha activity may be explained by the finding that alpha is generated in corticocortical pathways.11

There may be certain methodological limitations to our study. Although we made strenuous efforts to examine the effect of factors that could explain the relationship between EEG values and survival, the possible confounding effect of both clinical and neuroimaging features cannot be excluded. Vascular risk factors and indicators of atherosclerosis, recently implicated in the pathogenesis of AD,43 may especially be associated with EEG abnormalities and they may also play a role in the prognosis. We examined leukoaraisis on CT, but more sensitive assessment of white matter abnormalities and hippocampal atrophy is possible with magnetic resonance imaging. Further, we used presence of diseases associated with vascular risk, but no quantified measures of atherosclerosis were used. A recent study suggested that patients with AD homoyzous for apolipoprotein E4 allele had selective decreases in functional connectivity, assessed with EEG coherence in the alpha frequency band, compared with those without or with only 1 apolipoprotein E4 allele.44 Although several studies did not find an association between apolipoprotein E genotype and survival in AD,13,31 another study reported that the presence of at least 1 apolipoprotein E4 allele reduced the risk of mortality in AD.37 These results suggest that the role of apolipoprotein E genotype, subclinical vascular disease, and AD progression in relation to EEG findings need further examination. Medication in our patients probably did not play a role, since exclusion of those with centrally active medication yielded similar results. Recently, efforts were made to construct prediction algorithms based on clinical features, including age at onset, presence of extrapyramidal or psychotic symptoms, and levels of cognitive function.6 Since we used these features as correction factors, our results suggest that the EEG should be used as an additional variable in future endeavors to construct a predictor index.

In conclusion, decreased beta and decreased alpha activity on EEG are predictors of survival in patients with early AD, independent of demographic, clinical, and CT features, including leukoaraisis and cortical atrophy. These results suggest that the EEG should be included as an independent variable in survival models of AD. However, the use of the EEG for prediction of survival in individual patients in clinical practice remains to be determined.

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