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Generators of brain electrical activity in patients with Wilson's disease

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Abstract Electroencephalographic (EEG) generators were investigated in 13 patients suffering from hepatolenticular degeneration with and without neurological symptoms and in 13 healthy subjects for comparison by the use of FFT approximation. Quantitative assessment of motor deficits and psychiatric disturbances was correlated with EEG features. We found mainly an increase in delta activity, a decrease in alpha activity combined with a more posterior localisation of the EEG generators in the delta band and a more anterior one in the alpha band in patients compared with healthy controls. The localisation of the EEG generators in the patients with clinical apparent neurological symptoms were in all frequency bands more superficial compared with controls and patients without neurological symptoms. With longer duration of the disease, the lower the premorbid intelligence the more posterior was the delta EEG generator localised. Although the alpha EEG generator was more anteriorly localised with longer duration of the disease and more severe cognitive deficits, it was more superficial with more pronounced psychiatric symptoms, more severe cognitive deficits, lower premorbid intelligence and more pronounced motor disabilities. With more pronounced psychiatric symptoms and cognitive deficits, the beta EEG generator was more anteriorly localised. The present study demonstrated that a significant deviant EEG pattern exists between patients with and without clinical neurological symptoms and that stage-dependent alterations in psychiatric symptoms and cognitive ability are reflected on the EEG.

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Introduction

Wilson's disease (WD) is an autosomal-recessive inherited disorder characterised by accumulation of copper in the liver, brain, kidney and cornea (Scheinberg and Sternlieb 1984). The genetic locus for the WD gene has been assigned to 13q 14-21 and the gene product has been identified as copper transporting P-type ATPase (Bull et al. l993; Petrukhin et al. 1993; Tanzi et al. 1993). Neurological and psychiatric manifestations result from lesions both in the basal ganglia and in occipital, frontal and prefrontal areas of the brain (Starosta Rubinstein et al. 1987; Hawkins et al. 1987; Horoupian et al. 1988). Brain atrophy and low-density areas have also been documented by computed tomography and magnetic resonance imaging (Williams and Walshe 1981; Chen et al. 1983; Prayer et al. 1990; Roh et al. 1994). In addition, neurophysiological studies have shown that subclinical sensory dysfunction is common in WD, and that auditory and somatosensory pathways are most severely affected at the brainstem level (Roach et al. 1985; Berardelli et al. 1990; Selwa et al. l993). In contrast, no indication of specific alterations in conventional EEG has been reported; however, it was suggested that the degree of possible EEG abnormalities correlates with the severity of the disease (for review see Heller and Kooi 1962).

Regarding the quantification of multi-channel EEG recordings, the most common method for EEG quantification Fast Fourier Transform (FFT) has various disadvantages. The huge amount of dependent variables makes a confirmative statistical analysis problematic. Furthermore, as Lehmann (1989 a) has pointed out, FFT-power data are strongly dependent on the choice of recording reference. Consequently, the topographic distribution of brain electrical activity over the scalp in the frequency domain (FFT-power) varies considerably depending on the site of reference (Dierks et al. 1993 c). This shortcoming

is without consequences if data are used for stochastic classification of subjects only; however, a functional pathophysiological interpretation of data, which varies according to reference position, is obviously problematic.

To overcome the reference problem, Lehmann and Michel (1989b; 1990) presented a method to calculate equivalent dipoles in the frequency domain. The results gained by the FFT approximation are unambiguous with regard to reference, and results have been described for normals (Michel et al. 1992; Dierks et al. 1993d), in psychiatric diseases (Koukkou et al. 1991; Dierks et al. 1993a) and for psychopharmacological influence on electrical brain activity (Dierks et al. 1993b). Additionally, to the advantage of avoiding the reference problem, a simplification of brain electrical activity into one single centre-of-gravity equivalent dipole allows a more transparent statistical analysis of the data.

Recently, in a larger sample of Alzheimer disease patients, it was demonstrated that the localisation of dipoles gained by FFT approximation are related to the pattern of cerebral glucose metabolism assessed by positron emission tomography (Dierks et al. 1997).

The primary aim of the present study was to quantify possible EEG alterations in Wilson's disease both with and without neurological symptoms in comparison with healthy controls. Secondly, data obtained by multi-channel EEG should be evaluated further by correlation to motor, psychiatric and cognitive deficits. Of special interest also was the question of whether reversible cognitive impairment in patients with WD demonstrates patterns of EEG changes similar to those in other diseases with cognitive impairment, e.g. dementia of Alzheimer type (DAT), where the dementia is more or less irreversible.

Subjects and methods

Thirteen patients (mean age 31 ± 10 years, mean duration of disease 15 ± 9 years) suffering from WD were studied. The diagnosis was based on reduced serum ceruloplasmin and serum copper levels, increased copper excretion in 24-h urine samples and either on high copper content in a liver biopsy specimen or on pathological radio-copper test (Wesch et al. 1980). During the study 5 patients were free of neurological and psychiatric symptoms. In 8 patients neurological examination revealed dysarthria ($n = 6$), resting or action tremor ($n = 4$), bradykinesia ($n = 4$) or oculomotor dysfunction ($n = 2$). Quantitative assessment of neuropsychological, psychiatric and motor deficits was performed with a battery of tests: (a) the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) for assessment of psychiatric symptoms; (b) the Brief Cognitive Rating Scale (BCRS; Reisberg et al. 1983) for assessment of cognitive functions; (c) Mehrfachwortschatz-Intelligenztest; (MWTB; Lehrl 1976) for assessment of premorbid intelligence; (d) Columbia University Rating Scale (CURS; Duvoisin 1970) for assessment of Parkinsonian symptoms; and (e) Abnormal Involuntary Movement Scale (AIMS; Guy 1976) for assessment of dyskinesia. All patients were treated with D-penicillamine (900–2100 mg daily) and a preparation of copper-free metals (biometalle III, two times per week). One patient additionally received I-dopa benserazide (200/50 mg daily), bromocriptine (5 mg daily) and I-deprenyl (5 mg daily). None of the patients exhibited any clinically apparent hepatic dysfunction.

For comparison with the patient group, 13 healthy subjects were selected (mean age 29 ± 5 years). They were screened to exclude subjects with neurological or psychiatric disorders, drug or alcohol dependence, head injury and use of psychopharmacologically active medication. All controls and patients were right handed.

Data acquisition

Silver-silver chloride cup electrodes were applied at 20 sites to the scalp according to the international 10–20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, and O2). The EEGs were recorded referred to linked mastoids with compensating resistors of 10 kOhm on each side. The electrode localisations were cleaned to ensure low impedances and the electrodes were fastened by paste. Prior to the recording, the impedances were measured, and low and similar values were ensured in all channels (in each channel lower than 3 kOhm and interelectrode difference lower than 1 kOhm). The subjects were lying comfortably on a bed with their eyes closed. All subjects were investigated in the morning and the EEG was monitored for changes in vigilance by an experienced EEG technician. Data were recorded with a 20-channel Brain Atlas III Plus (Bio-Logic, Mundelein, USA). The EEG was sampled at a rate of 128 Hz per channel and stored onto magnetic disks for further analysis off-line. Before AD conversion, the EEG was filtered analogously with a band pass of 1.0–30.0 Hz.

Overall amplification was 20,000 times. For data analysis the first ten successive artefact-free 2-s periods, 20 s after eyes were closed, were selected off-line from the stored spontaneous EEG. Previous studies have indicated that EEG periods of 20-s duration are sufficient to be representative for the whole EEG under presumption of a steady state (Mocks and Gasser 1984).

Data processing – FFT dipole approximation

Fast Fourier analysis was done on each 2-s period. The resulting sine and cosine coefficients for each electrode and each frequency point (0.5-Hz resolution) were placed into a sine-cosine diagram (Lehmann et al. 1986). All entries in the sine-cosine diagram are orthogonally projected upon a "best-fit" line, which is equivalent to the first component of a principal component analysis (PCA). The projection of the entries in the sine-cosine diagram on the best-fit line is called FFT approximation (Lehmann and Michel 1989b) and describes a map of potential distribution, which is used for estimation of the equivalent dipole source which gives the least-deviation set of dipole field amplitudes.

For equivalent-dipole source localisation, a moving (instantaneous) equivalent current dipole (ECD) and a three-shell-head model in which there were no constraints of the dipole parameters was used (Kavanagh et al. 1978). For each frequency point in the FFT approximation, and thus for each frequency in the spectrum, a "centre of gravity" localisation for the brain electrical activity was calculated with four resulting parameters: (a) magnitude (μV), (b) right-left (mm) localisation; (c) anterior-posterior (mm) localisation, and (d) depth (mm). The information regarding the orientation of the dipoles is not presented here. The localisations were expressed as distance from the middle point of a spherical head model (zero value; 10% level in the 10–20 system; positive values are anterior, superficial and left of the zero value). For a detailed description and discussion of these methods see Lehmann and Michel (1989b; 1990), Michel et al. (1992) and Dierks et al. (1993c).

Statistical analysis

The localisation of equivalent dipoles in control subjects as well as in patients followed a normal distribution (Kolmogoroff-Smirnoff test), entitling the use of parametric statistical tests. All calculations were performed using the SPSS-PC statistical package.

For statistical purposes, data were reduced into frequency bands. A mean magnitude localisation of the equivalent dipole

were calculated for delta (2.0–3.5 Hz), theta (4.0–7.5 Hz), alpha (8.0–11.5 Hz), beta1 (12.0–15.5 Hz), beta2 (16.0–19.5 Hz), and beta3 (20.0–23.5 Hz) for each subject. The cut-off frequency of 2.0 Hz for the delta band was chosen to avoid any influence of slow-wave artefacts on the results. Thereafter, a two-factorial ANOVA for repeated measurements over frequency bands was carried out for the four independent variables (magnitude and localisation). The factors used were (a) group (control, patients with no neurological and patients with neurological symptoms; df = 2,23), and (b) frequency band (1–6; repeated measurement; df = 5,115). The calculation of significant effects was corrected for degrees of freedom (Geisser and Greenhouse 1958). Post hoc was a one-way ANOVA performed in each frequency band. In this way, a conservative test was used to investigate differences. For the exploratory investigation of relations between equivalent dipole and clinical parameters, Pearson's linear correlation was calculated (df = 24).

Results

Results regarding differences in brain electrical activity between the control group and the group of patients with Wilson's disease

For the factor group, overall significant statistical effects were found with regard to depth of the mean ECD in the three groups. Overall significant statistical effects were also found for factor frequency band for the variables magnitude, anterior-posterior direction and depth. Moreover, a statistically significant interaction between factor group and factor frequency band was observed in magnitude and in anterior-posterior direction. Regarding the left-right direction, no significant differences between mean ECD localisations in the three groups, nor between the frequency bands, were detected, and neither was the interaction between the factors group and frequency band significant (Table 1).

Delta band (2.0–3.5 Hz)

Significant results were obtained with regard to magnitude (F = 3.9, p = 0.035). The patients with WD showed higher magnitudes compared with the healthy control group, and additionally, the patients with neurological symptoms demonstrated a somewhat higher magnitude compared with the patients without neurological symptoms (Fig. 1). The mean ECD was more posteriorly localised in patients with WD compared with the control group (F = 3.7, p = 0.041). The patients with neurological symptoms showed a deeper localisation of the dipole compared with the healthy group and the group of patients without neurological symptoms (Fig. 2 a).

Theta band (4.0–7.5 Hz)

No significant differences between the healthy control group, the patient group without neurological symptoms and the one with neurological symptoms was observed (Figs. 1, 2 b).

Alpha band (8.0–11.5 Hz)

The magnitude of the mean ECD in patients with hepatolenticular degeneration was lower compared with the one in the healthy control group (F = 6.7, p = 0.016; Fig. 1). However, between the patients without neurological and patients with neurological symptoms, no difference was observed. The ECD was slightly more anteriorly localised in the patient groups (F = 2.8, p = 0.10), and most pronounced in the group with neurological symptoms in which group the ECD was additionally slightly more superficial compared with the other groups (Fig. 2 c).

Beta1 band (12.0–15.5 Hz)

No significant differences between the healthy control group, the patient group without neurological symptoms and the one with neurological symptoms was observed (Figs. 1, 2 d).

Beta2 band (16.0–19.5 Hz)

A tendency of more anteriorly and superficially localised mean ECD in the patient groups was observed, with the dipole in the group with neurological symptoms the most anterior and superficial one (Fig. 2 e).

Beta3 band (20.0–23.5 Hz)

The mean ECD in the patient group with neurological symptoms was significantly more superficially localised

Table 1 Resulting F-values and p-values of the repeated-measurement ANOVA with regard to magnitude and localisation of equivalent dipoles between the control group, the group of patients without and the group with neurological symptoms for the factors group (df = 2,23), and frequency band (df = 5,115), and for the interaction between the two factors (df = 5,115)

Dipole parameter	Group		Frequency band		Group × frequency band	
	F-value	p-value	F-value	p-value	F-value	p-value
Magnitude	0.12	0.89	28.23	< 0.001	3.44	0.01
Left-right	1.91	0.17	0.9	0.99	1.87	0.10
Anterior-posterior	0.6	0.56	27.93	< 0.001	2.60	0.02
Depth	3.57	0.04	3.07	0.03	1.23	0.30

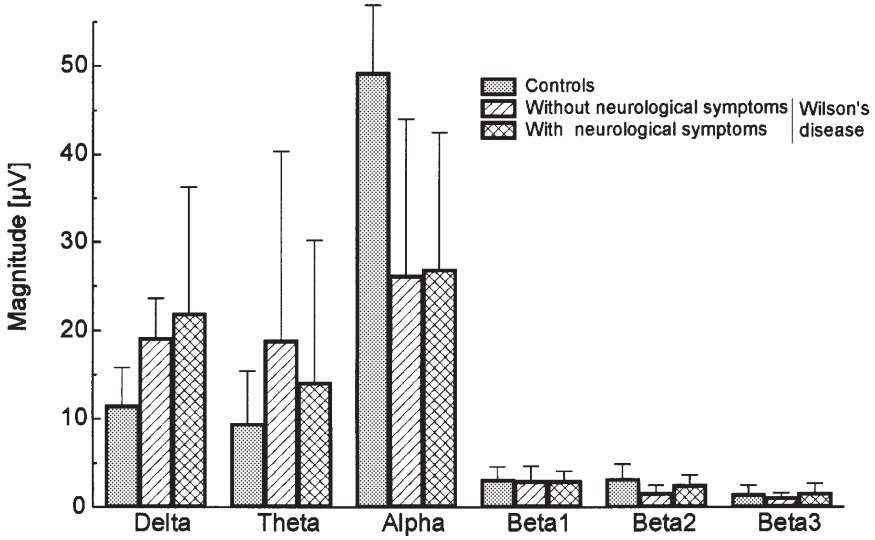

Fig. 1 Mean values and standard deviations of equivalent dipole magnitude in the delta (2.0–3.5 Hz), theta (4.0–7.5 Hz), alpha (8.0–11.5 Hz), beta1 (12.0–15.5 Hz), beta2 (16.0–19.5 Hz) and beta3 (20.0–23.5 Hz) bands for the healthy control group (n = 13) and the group of patients without neurological symptoms (n = 5), and the group with neurological symptoms (n = 8)

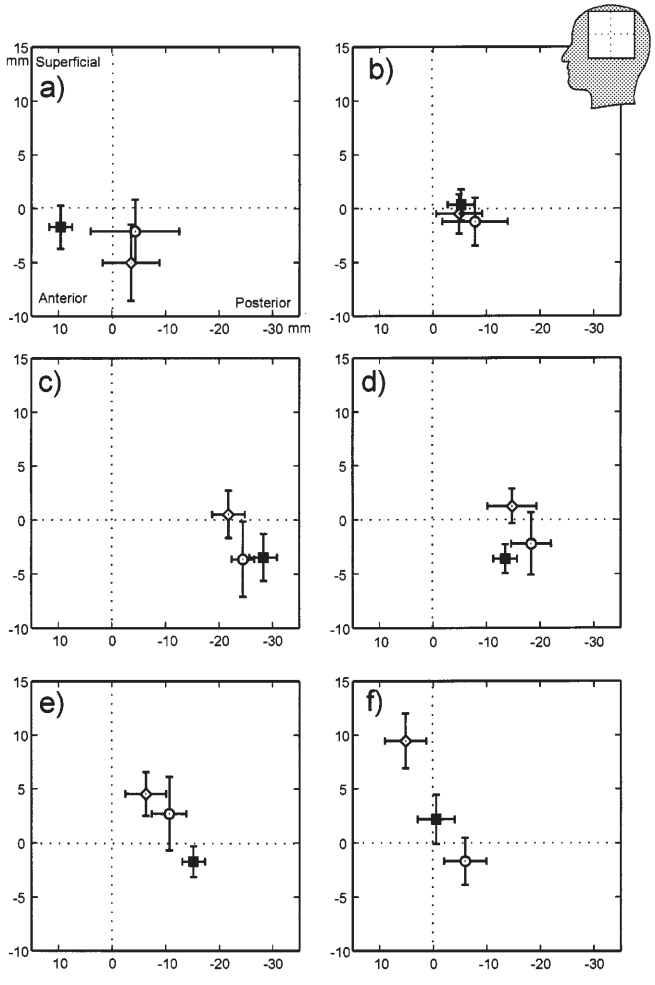

Fig. 2 a–f Two-dimensional plot of mean values and standard errors of equivalent dipole localisations in anterior-posterior direction and for the depth in the **a** delta (2.0–3.5 Hz), **b** theta (4.0–7.5 Hz), **c** alpha (8.0–11.5 Hz), **d** beta1 (12.0–15.5 Hz), **e** beta2 (16.0–19.5 Hz), and **f** beta3 (20.0–23.5 Hz) bands for the control group (*squares*) and the group of patients without neurological symptoms (*circles*), and the group with neurological symptoms (*diamonds*)

compared with the one in the control group and in the patient group without neurological symptoms (Fig. 2 f).

Correlation between ECD parameters and psychiatric- and psychometric tests in patients with Wilson's disease

Delta band

A significant negative correlation between magnitude (r = –0.42, $p < 0.05$) and localisation (r = –0.61, $p < 0.01$) of ECD and duration of the disease was observed, indicating that a longer duration of the disease is associated with more posteriorly localised ECDs with lower magnitude. Regarding psychometric tests, the MWTB test (premorbid intelligence) correlated significantly negative with the magnitude (r = –0.43, $p < 0.05$) and positive with the localisation of the ECD in anterior-posterior direction (r = 0.67, $p < 0.01$). The magnitude of ECD correlated positively with severity of parkinsonian symptoms (CURS; r = 0.41, $p < 0.05$) and the depth of the ECD correlated positively with severity of dyskinesia (AIMS; r = 0.42, $p < 0.05$).

Alpha band

A significant positive correlation was observed between duration of disease and localisation of the ECD in anterior-posterior direction (r = 0.57, $p < 0.01$). Furthermore, the BCRS score (cognitive impairment) correlated significantly positively with localisation of the ECD both in anterior-posterior direction (r = 0.44, $p < 0.05$) and in depth (r = 0.53, $p < 0.01$). Also the MWTB score (premorbid intelligence) correlated significantly negatively with the depth of the dipole (r = –0.68, $p < 0.01$). Severity of parkinsonian symptoms (CURS) correlated significantly positively with depth (r = 0.63; $p < 0.01$).

Beta3 band

Of the psychometric tests, the BCRS score (cognitive impairment) correlated significantly positively with the magnitude of the ECD ($r = 0.46$, $p < 0.05$), BPRS (psychiatric symptoms) ($r = 0.83$, $p < 0.01$) and BCRS ($r = 0.73$, $p < 0.01$) score correlated significantly positively with the localisation of the ECD in anterior-posterior direction and the MWTB (premorbid) intelligence ($r = –0.40$, $p < 0.05$) and BCRS score ($r = 0.43$, $p < 0.05$) correlated significantly with the depth of the dipole. The CURS score correlated significantly positively with the localisation in anterior-posterior direction of the ECD ($r = 0.64$, $p < 0.05$), and the AIMS score correlated significantly positively with the depth of the dipole ($r = 0.41$, $p < 0.05$).

Discussion

There are only a few reports of quantitative EEG in WD, and to our knowledge, there are no prior report on quantified topographic EEG alterations. In general, previously published results regarding EEG and WD have been based on conventional EEG recordings. Hansotia and co-workers (1969) reported normal and abnormal EEG of approximately the same proportion in patients with only hepatic symptoms as well as in patients with neurological symptoms, and they furthermore concluded that in the case of abnormal EEG, no clear correlation between clinical or biochemical parameters and EEG features did exist. Nevsimalova and co-workers (1986), on the other hand, reported mostly abnormal EEG recordings both in patients with neurological symptoms and in patients with only hepatic symptoms. This is consistent with results published by Sack and co-workers (1975) where they described a high degree of EEG alterations already in the prodromal asymptomatic stage of the disease.

Nevsimalova and co-workers (1986) additionally reported non-significantly more severe abnormal EEG findings in patients with neurological symptoms compared with patients with only hepatic symptom. The most common reported abnormal EEG feature in WD is increased slow-wave activity. In the present study we could, by using quantitative EEG, confirm these findings and additionally show that certain EEG alterations are related both to neurological and psychiatric symptoms in WD.

In dementia of Alzheimer type (DAT), a disease which, in contrast to WD, leads to irreversible cognitive impairment, increased amplitude of delta and theta activity has been reported to correlate with increasing severity of cognitive impairment (Penttilä et al. 1985; Dierks et al. 1991).

In the present study no correlation between cognitive impairment and magnitude of the delta ECD was found. However, the magnitude of the delta ECD was increased in patients with WD compared with controls with the highest one in the patients with neurological symptoms. In patients with WD the delta ECD was more posterior, and in the group of patients with neurological symptoms, more deeply localised, whereas in a previous study we found no differences between healthy control subjects and DAT patients with regard to localisation of the delta ECD (Dierks et al. 1993 c). Since the EEG is most likely cortically generated and a more widespread cortical electrical activity will result in more deeply estimated single dipoles, a deeper localisation will consequently have to be interpreted as more widespread activity. The subcortical degenerative alterations in putamen and caudate nucleus in WD may lead to the reported generalised alterations of slow-wave activity, whereas in DAT the NbM (nucleus basalis Meynert) with its cholinergic innervation is most affected, leading to a stage-dependent alteration of slow-wave ECD magnitude in a different way compared with WD. Regarding possible effects of medication, penicillamine have been discussed to be related to epileptic graphoelements occurring in WD (Nevsimalova et al. 1986). We did not find any epileptic graphoelements in the investigated patients.

The results regarding the correlation between psychiatric and psychometric tests confirms our previous investigations indicating that the EEG reflects alterations of the psychopathological and cognitive state of patients (Dierks et al. 1991; 1995). Similar to dementia of Alzheimer type we found more anterior ECD in the alpha band with increasing cognitive impairment, indicating that this parameter could be sensitive to alterations in cognitive ability. Whereas in DAT a strong correlation between beta ECD magnitude and cognitive performance existed (Dierks et al. 1993 c), this was not the case in patients with WD. This suggest that changes in alpha frequency band could be characteristic of functional disturbances of cognition, and that alterations in beta frequency band could be more specific for DAT. Recently, it was demonstrated that a correlation exists between the spatial pattern of glucose metabolism and the localisation of ECD alpha activity in a larger sample of DAT patients (Dierks et al. 1997); thus, the present finding of a significantly reduced amplitude of ECD alpha activity and a comparably less apparent change of spatial localisation may be due to the described globally reduced cerebral glucose metabolism which occurs in WD (Kuwert et al. 1992); however, a significant age difference between patients with WD and DAT patients has to be considered as a possible reason for the differences between both groups.

The present study demonstrated, contrary to most previous conventional EEG investigations of WD, that a significantly different EEG pattern exists in patients without clinical neurological symptoms and patients with neurological symptoms. Furthermore, the investigation showed that stage-dependent alterations of psychiatric symptoms and cognitive ability are reflected on the EEG. The use of appropriate quantitative EEG analysis may hence allow an objective non-invasive and easily available tool for clinical staging during the treatment of WD.

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