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Quantitative EEG Findings in Patients with Chronic Renal Failure

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Abstract
Objective: Chronic renal failure frequently causes uremic encephalopathy with impairment of various cognitive functions, but the pathophysiology of uremic syndrom is complex and poorly understood. In this study, we wished to establish a reliable tool and monitor system to evaluate the central nervous system dysfunction of patients with uremic encephalopathy.
Methods: A group of 31 patients with chronic renal failure was assessed with online real time brain mapping using the CATEEM technology to detect deviations and abnormal EEG patterns. Quantitative EEG data were compared with those of an age-matched healthy control group and correlated to laboratory markers and various dosages of erythropoietin.
Results: Electrical power was most prominent in delta, theta and alpha frequencies in the temporal and central brain areas (electrode positions T5, T6, C3 and C4). Explorative statistical comparison of the two data sets with respect to these brain areas revealed that the increases in electrical power in delta, theta and alpha frequency bands were different from healthy people with p-values of $p<0.003$ (delta), $p<0.0003$ (theta), $p<0.01$ (alpha 1) and $p<0.01$ (alpha 2). In addition, high levels of hemoglobin were significantly correlated with higher theta activity.
Conclusion: We detected distinct EEG deviations from normality in patients with chronic renal failure. Online real time brain mapping using the CATEEM technology provides a unique possibility to monitor mental impairment and serves as a control for therapeutical intervention.

Key words: Quantitative EEG, Uremic Encephalopathy, Erythropoietin, Anemia, Hemodialysis

Introduction

Patients with chronic renal failure frequently manifest complications of the central nervous system (CNS) such as uremic encephalopathy with impairment of neurological and neurobehavioral function [1]. The characteristics of the uremic syndrome can be quantified by electrophysiologic and psychometric methods, but the pathophysiology of uremic encephalopathy is complex and poorly understood [2-6]. Conventional electroencephalography in chronic renal failure reveals nonspecific EEG slowing, especially slowing of the alpha rhythm in the early stages of renal disease, with a more dramatic downward shift in the dominant frequency from alpha toward theta as renal failure progresses. This is best seen as changes in the distribution of power in the computerized EEG frequency spectrum [7]. Previous studies have shown that quantitative EEG and brain mapping are powerful tools to evaluate the central nervous system dysfunction [8-10]. Sagalés and co-workers demonstrated that the power spectral density related amplitudes and frequency of the electrical waves originating from cerebral activity were clearly depressed in patients with chronic renal failure. The distribution of power among the frequency bands was also abnormal [11].

Chronic hemodialysis corrects the symptoms of chronic renal failure, but neuropsychological and electrophysiological studies have quantitatively documented the incomplete reversal of CNS and cognitive function abnormalities [12-14]. The persistence of mild neurobehavioral impairment suggests that uremic toxins are probably not the sole cause of altered brain function. Since anemia is almost always present in patients with chronic renal failure, due to a decrease in erythropoietin production by the failing kidney, it has been suggested that anemia could play a substantial role by affecting cerebral oxygen delivery [15]. Several studies showing improved brain and cognitive function after treatment with recombinant human erythropoietin (rHuEPO) have already been published, but the lack of full neurological normalization suggests that factors other than anemia also account for the neurobehavioral dysfunction of patients with chronic renal failure [1, 5, 11, 16, 17]. Renal failure results in an accumulation of numerous organic substances that possibly act as uremic neurotoxins, but no single metabolite has been identified as the sole cause of uremia [18]. Furthermore, hormonal disturbance, disturbance of the intermediary metabolism and imbalance in excitatory and inhibitory neurotransmitters have been identified as contributing factors.

The aim of the present study was to assess dialysis patients with online real time brain mapping using the CATEEM technology (see methods) to detect deviations and abnormal EEG patterns. We wished to establish a reliable tool and monitor system to evaluate the central nervous system dysfunction of patients with uremic encephalopathy. Therefore, we evaluated the state of EEG activity by frequency analysis of the ongoing EEG. The EEG data were compared by explorative statistics with those of a healthy control

Table 1. Average electrical power in % of total power within each frequency (median) for the combined electrode positions C3+C4+T5+T6 from all patients in comparison to hemoglobin (g/dl) values and rHuEPO dosage (IU).

		Dialysis Patients						
Pat. #	**Hemoglobin**	**rHuEPO**	**delta**	**theta**	**alpha1**	**alpha 2**	**beta 1**	**beta 2**
1	8.2	6000	104	75	121	128	141	129
2	8.7	0	89	80	105	111	92	78
3	10.0	12000	74	86	146	108	100	99
4	9.0	6000	87	74	78	90	93	65
5	9.9	15000	61	129	135	135	149	107
6	9.9	6000	122	100	107	103	102	101
7	10.8	6000	80	121	90	115	115	121
8	12.0	6000	78	89	146	114	145	136
9	10.2	6000	97	117	138	162	143	111
10	9.4	6000	67	96	82	122	120	116
11	11.3	12000	116	103	112	124	129	113
12	10.8	6000	114	154	180	114	98	92
13	9.0	6000	77	81	106	83	93	101
14	9.9	6000	92	103	118	107	146	136
15	9.3	12000	82	83	130	99	105	98
16	11.0	12000	99	112	148	109	134	112
17	11.4	0	68	100	138	94	107	81
18	10.0	6000	92	100	89	110	89	94
19	10.8	2000	106	110	112	127	137	113
20	10.9	9000	93	101	105	94	92	76
21	10.6	0	121	100	104	104	93	65
22	12.6	18000	78	152	147	190	111	111
23	11.2	12000	108	116	87	112	103	101
24	11.0	12000	83	86	93	82	96	88
25	11.4	6000	116	118	119	101	124	94
26	13.5	6000	121	93	118	121	132	141
27	14.0	0	96	103	104	92	106	98
28	10.5	6000	79	105	119	110	106	78
29	9.6	0	90	85	166	134	144	75
30	11.5	12000	137	213	169	144	154	115

Table 2. Statistical comparison of 30 dialysis patients with a normal healthy group of 95 subjects. Data are given for the three subsets of data and for the total group. No rHuEPO (n=5); Low rHuEPO (n=15): < 6000 IU/week; High rHuEPO (n=10): > 6000 IU/week. The combined electrode positions (C3,C4 and T5,T6) are calculated. Wilcoxon-Mann-Witney U test on the base of absolute spectral power values.

	Electrode positions C3, C4 and T5, T6		
rHuEPO	**delta**	**theta**	**alpha 1**
high	0.0000334	0.0000095	0.0134830
low	0.0035738	0.0180406	0.1099767
no	0.1945472	0.1603585	0.0189913
all	0.0000030	0.0000069	0.0013623

group and correlated to laboratory data (creatinine and hemoglobin) and various dosages of rHuEPO.

METHODS

SUBJECTS

A group of 31 patients (14 females and 17 males; age range: 21 to 84, median 65 years) with chronic renal failure undergoing center hemodialysis for the last 6 months has been studied. The original diagnoses were: diabetic nephropathy (N = 10), nephrosclerosis (N = 2), interstitial nephropathy (N = 3), chronic glomerulonephritis (N = 2), chronic pyelonephritis (N = 2), toxic nephropathy (N = 2) and acute renal failure (N = 3). Chronic renal failure was not typified in 7 cases.

All patients had been undergoing hemodialysis treatment thrice weekly during the six month period prior to investigation. Despite a constant dialysis time, dialyzer, and blood flow resulting in a KT/V of at least > 1.1, the patients received standard therapy concerning blood pressure, acidosis treatment, Vitamin D supplementation. The residual renal function of all patients was below 500 ml/day. None of them had primary central nervous system disease or uncontrolled arterial

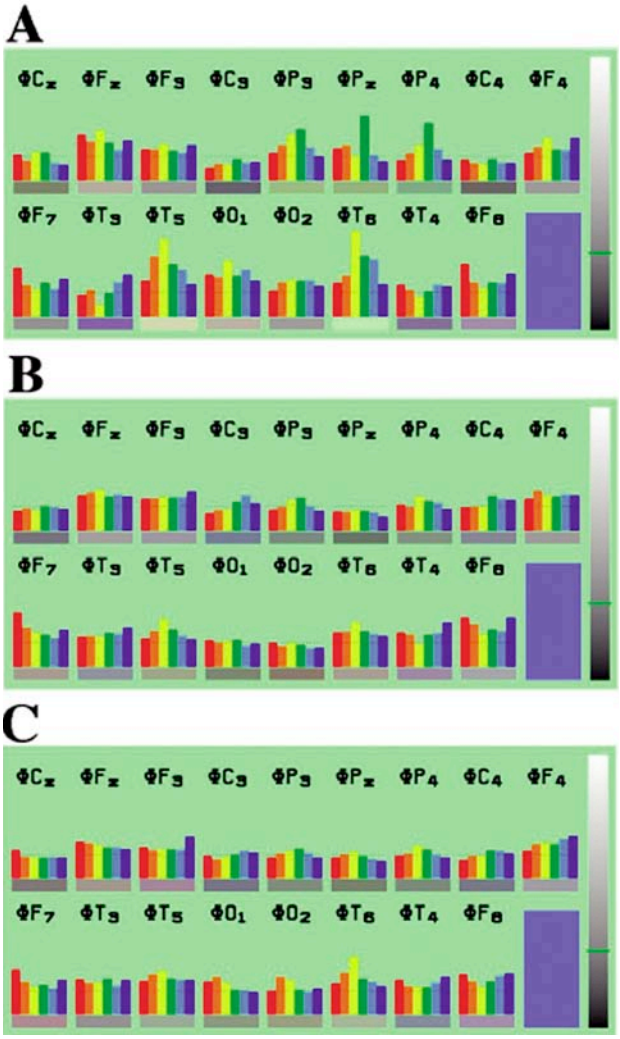

Fig. 1. Recordings on intradialytic days with respect to frequency distribution under the recording condition eyes closed. Separation of the group of patients according to treatment with rHuEPO. No rHuEPO (1A: n=5); Low rHuEPO: <6000 IU/week (1B: n = 15); High rHuEPO: >6000 IU/week (1C: n = 10). Total electrical power within one frequency range is set to 100 %. Each electrode position (see bar graphs) reflects the percentage of total power (spatial normalization, designated as % G). The dashed line indicates 100%. Electrode positions: C = central, F = frontal, P = parietal, O = occipital, T = temporal. Frequencies are depicted from left to right: delta, theta, alpha1, alpha2, beta1 and beta2.

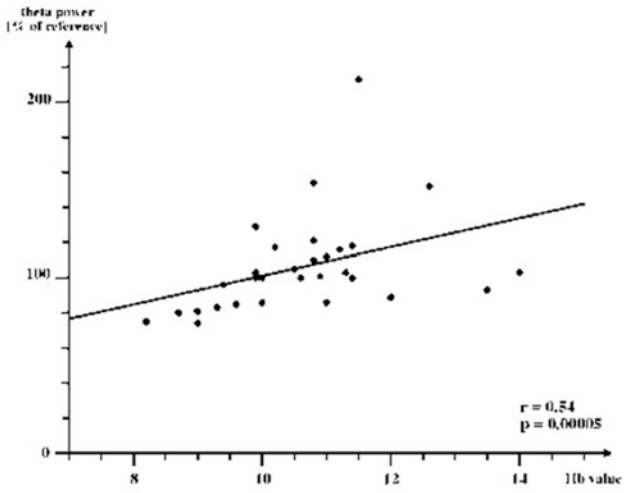

Fig. 2. Correlation between Hemoglobin values and EEG theta power at the combined electrode positions C3+C4+T5+T6. Electrical power in delta, theta and alpha frequencies in the temporal and central brain areas (electrode positions T5, T6, C3 and C4) were most prominent.

hypertension (RR syst. >160 and diast. >110). Mean hemoglobin values were 10.6 g/dl (range: 8.2 to 14.0 g/dl). Twenty five patients received various dosages of intravenous rHuEPO-α or rHuEPO-β (2000-18000 IU/week) (Table 1). A day in between hemodialysis treatment was selected to perform the explorations.

The number of patients investigated was small and, due to the heterogenous patient population, a subgroup analysis was not performed (diabetic patients vs. non-diabetic patients, antihypertensive medication).

Quantitative EEG

The EEG was recorded bipolarly from 17 surface electrodes according to the international 10/20 system with Cz as a physical reference electrode (Computer aided topo-graphical electro-encephalo-metry: CATEEM® from MediSyst GmbH, 35440 Linden, Germany), using an electrocap. The raw signals were amplified, digitized (2048 Hz/12 bit) and transmitted via fiber optical devices to the computer. The automatic artefact rejection of the CATEEM®-System, which eradicates EEG-alterations caused by eyeblinks, swallows, respiration, ect. during the recording was automatically controlled and individually adjusted by the investigator. EOG was recorded in one channel in order to facilitate detection of signals superposing onto the EEG. The artefact rejection set-up was observed for about 5 minutes prior to the start of recording to ensure that all artefacts were correctly eliminated from further evaluation. For safety purposes the original raw data was saved on optical disk in order to allow re-evaluation of the artefact rejection mode if necessary. In these cases the experimental session was re-examined offline with a newly adapted rejection mode. The amount of rejected data was determined automatically and given in percent of total recording time. Nevertheless, the entire recording and the computer-based automatic artefact rejection were continuously supervised and adjusted by a trained physician. The data was recorded under two physiological conditions over a period of 5 minutes each (eyes open and eyes closed). Due to artefact contamination only the data from the eyes closed condition were analyzed.

The signals of all electrode positions underwent Fast Fourier Transformation (FFT) based on 4-second sweeps of data epochs (Hanning window). Data were analysed from 0.86 to 35 Hz using the CATEEM® software. In this software the resulting frequency spectra are divided into six frequency bands: delta (1.25 - 4.50 Hz), theta (4.75 - 6.75 Hz), alpha1 (7.00 - 9.50 Hz), alpha2 (9.75 - 12.50 Hz), beta1 (12.75 - 18.50 Hz) and beta2 (18.75 - 35.00 Hz). This frequency analysis is based on absolute spectral power values. Electrical

power within each frequency band was summed up from all electrode positions and set to 100%. Spatial redistribution gave relative normalized values for each frequency and electrode position. Subsequently, a median group file was built based on the results of single patient analysis for documentation and explorative statistical analysis.

Statistical Analysis

For explorative statistical comparison of the patient EEG data to those of an age related healthy control group the non-parametrical Wilcoxon test was used. In order to form these groups, EEGs of at least 95 healthy volunteers each were recruited and gathered in the age groups 20 to 50 years and older than 50 years respectively. All volunteers included in these control groups underwent a thorough clinical and neurological examination as well as biochemical and haematological blood testing, all of which had to be inconspicuous of any other kind of disease for a volunteer to be considered "healthy". In both groups a non-parametric estimation of the distribution of EEG power values for each frequency band at each electrode was performed. This allowed us to compile a "normal range" for EEG data and to compare the patients EEG data to it. Data were successfully analyzed for n= 30 subjects. For all patients hemoglobin values and creatinine values (30 patients) were available.

Results

A total of 31 patients had been recorded under the condition of eyes open and eyes closed, respectively, but only data from the eyes closed condition were analyzed (one patient did not give valuable recordings). Abnormal findings are mainly seen with respect to alpha1 power at the temporal electrode positions T5 and T6. Explorative statistics revealed significant increases of alpha1 power in comparison to the control group. Delta and theta activity was also increased.

In order to find a common denominator the data from all patients were averaged to create three group data sets according to treatment with recombinant human erythropoietin. The result is depicted in Fig. 1 in bar graphs showing the median values of electrical power for each electrode position. From the depiction of changes at certain electrodes it is obvious that a common denominator of electrical changes can be found at the electrode positions T5 and T6. From numerical statistical analysis for each electrode position it also appeared that there were common changes in the central area represented by the electrode position C3 and C4. Therefore data from this brain area including the positions T5, T6, C3 and C4 were averaged to give one value which now also could be compared to a data base containing healthy subjects. On the base of the raw data of 30 patients the data set was compared to a data base containing records of 95 healthy people. Explorative statistical comparison of the two data sets with respect to this defined brain area revealed that the increases in electrical power in delta, theta and alpha frequency bands were different from those of healthy people with p-values of $p<0.003$ (delta), $p<0.0003$ (theta), $p<0.01$ (alpha 1) and $p<0.01$ (alpha 2). Table 2 also gives information on the three subsets of data according to treatment with rHuEPO.

The most pronounced increases in electrical power were seen for the alpha 1 frequency band which is documented in Table 1 (for statistics see Table 2). Patients treated with rHuEPO displayed significantly higher theta and also delta power than the five untreated patients in comparison to healthy subjects.

We also performed a correlation analysis between the above findings and laboratory data measured in the present study (hemoglobin and creatinine). For delta and theta activity there is a correlation to hemoglobin values but hardly to creatinine values (data not shown). Results for single patients are documented in Table 1. The correlation between hemoglobin values and theta activity was highest with $r = 0.54$; $p<0.00005$ (Fig. 2) whereas delta power correlated only very weakly with hemoglobin values ($r = 0.28$; $p<0.11$, not shown). In addition, theta power correlated with the dosage of rHuEPO ($r = 0.3$; $p<0.07$, not shown).

Discussion

Patients with chronic renal failure frequently manifest complications of the central nervous system with complex neuropsychiatric symptomatology and cognitive dysfunctions. The question arises whether these patients can profit from additional pharmacological intervention and how this treatment can successfully be monitored with respect to a surrogate parameter closely related to their deficits. According to previous research functional brain parameters such as quantitative EEG and brain mapping are probably suited best. Online real time brain mapping using the CATEEM technology offers the opportunity to objectify cognitive deficits as shown in patients with dementia by a combination of EEG recording and concomitant psychometric evaluations [10]. The current analysis from 30 patients enforces this reasoning by providing evidence for mental deficits by means of quantitative electroencephalography.

Our data show, that patients with chronic renal failure did not exhibit an abnormal distribution of frequency band power when power for the different frequency bands was evaluated in the different brain areas. However, electrical power in alpha1 frequency was increased significantly in comparison to a group of normal subjects. Electrical power in delta, theta and alpha frequencies in the temporal and central brain areas (electrode positions T5, T6, C3 and C4) were most prominent. Highest increases were seen for the alpha 1 frequency band in temporal brain areas. This particular topographical cortical EEG-pattern was significantly different from normality with respect to alpha1 power and therefore could serve as a base for further investigations. Basic temporal alpha1 power reflects the status of attention. Thus, these higher alpha1 values can probably be interpreted as representing a deficit in the ability to concentrate.

In our study, high levels of hemoglobin were significantly correlated with higher theta activity. This correlation is high enough to conclude that changes of elec-

trical power in brain areas represented by the electrode positions T5, T6 and C3, C4 could reflect a metabolic pathophysiological finding. The weak correlation with the dosage of rHuEPO can possibly be seen in the same context. Therefore we must conclude that higher dosages of rHuEPO not only increase hemoglobin values but also increase theta power. Since theta power can be controlled by central norepinephrine this frequency possibly represents central control of the vegetative nervous system via Barrington`s nucleus [19]. It means that this increase reflects autonomic control. The pontine nucleus is a key component of a network that coordinates visceral activity with cognitive functions and behaviour [20].

These data seem to be in contrast to previous research, which in general show a nonspecific EEG slowing, with a more dramatic downward shift in the dominant frequency from alpha toward theta as renal failure progresses. The increase in EEG slowing could be reversed by partial correction of anemia with rHuEPO [7]. But one has to consider that data analysis in our study has been performed in a different way, in that electrical power was normalized by adding up each frequency to obtain the total power within one frequency band followed by a percent distribution for each electrode position. This means that we are talking about the individual topological distribution of single frequency power over the scalp. Comparison of these parameters with a group of normal subjects revealed the highly significant increase of alpha1 power in dialysis patients as described above. With respect to alpha frequencies we can assume that they could be involved in attention and memory, as can also be derived from the work of Gomez and Verstraeten [21, 22]. Thus, temporo-central alpha1 activity can be regarded as one of the parameters suitable for detecting subtle mental deficits.

Our study has several limitations. This analysis was not a controlled trial and the number of patients investigated was small. Furthermore, the patient population was heterogenous and we performed the electrophysiological measurements once only on interdialytic days. Our preliminary results could be the base for further evaluation of quantitative EEG analysis in uremia after adequate correction of anemia.

In summary, we detected distinct EEG deviations from normality in patients with chronic renal failure. In addition we succeeded in detecting local theta frequency changes obviously related to an increase of hemoglobin by the administration of rHuEPO. On the base of the current results it is tempting to suggest that online real time brain mapping using the CATEEM technology provides a unique possibility to monitor mental impairment and serves as a control for a therapeutical intervention. Since it was hypothesized that anemia is a contributor to the neurobehavioral dysfunction of uremia, several studies have shown improved brain and cognitive function after treatment with rHuEPO. For further prospective investigations the question arises whether rHuEPO leads to improved brain functions by correcting the anemia only or if a dose-dependent neuroprotective effect is present as has recently been reported for this drug [23]. In contrast to previous studies, Xenocostas et al demonstrated that rHuEPO crosses the intact human blood-brain barrier [24]. However, it remains to be determined whether rHuEPO may pass the blood-brain barrier in uremia and which rHuEPO dose is needed for a direct neuroprotective effect in patients with uremic syndrome.

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