

Original Article**Electroencephalogram findings in chronic kidney disease****Samir Tamer Abd- Allah¹, Doaa Mohammed Mahrous², Salwa Hussein Swelam³****Departments of Pediatrics, Faculty of Medicine, Minia University, El Minia, Egypt.****Abstract****Introduction**

Uremic polyneuropathy is a common complication of chronic renal insufficiency in the peripheral nervous system (PNS). EEG is useful in assessing patients with uremic encephalopathy and in monitoring their progress. EEG in CKD usually shows irregular low voltage with slowing of the posterior dominant alpha rhythm and occasional theta bursts. Prolonged bursts of bilateral, synchronous slow and sharp waves or spike waves are characteristic. These changes stabilize with dialysis when adequate, efficient of long duration and sufficient for appropriate urea clearance. However many patients as, hypertensive patients, those with associated electrolyte disorders (hypocalcemia, hypo or hypernatremia, hypo or hyperkalemia, intractable acidosis) will not show any improvement.

Aim of the study

To investigate the Electroencephalogram findings in different stages of chronic kidney disease.

Patients and Methods

In this prospective observational study, we included 54 children (22 males and 32 females) with different stages of chronic renal diseases (from stage 1 to stage 5, either in pre dialytic or dialytic stage), with mean age of 12.2 years & a range (4-18).

Results

Stages (3, 4 & 5) had significantly higher Theta pattern record compared to stages 1 & 2 (33.3% of both stage 3 & 4 and 50% of stage 5 cases have shown theta records. Increased frequency of asymmetry and sharp waves with progress of CKD to a maximum in dialytic stage.

Conclusions

Pediatric patients with chronic kidney diseases have obvious distinct EEG deviations from normality which increase with the progress of CKD.

Keywords

Chronic kidney disease, EEG, Uremic polyneuropathy

Running Title

Electroencephalogram findings in chronic kidney disease

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Introduction

According to the Kidney Disease Improving Global Outcome (KDIGO) guidelines, chronic kidney disease (CKD) is identified by the presence of kidney damage, either structural or functional, or by a decline in glomerular filtration rate (GFR) below 60mL/min/1.73m² of body surface area for more than 3 months. [1] The damage of kidney is defined as structural or functional abnormalities of the kidney or a large urinary tract infection causing a decrease in circulating blood to the kidney. [2] Markers of damage include abnormalities in the composition of the blood, abnormalities in the composition of the urine, and abnormalities in imaging studies. The GFR measures the flow rate of filtered fluid through the kidney. Normal GFR rates are 90-120 mL/min. [3]

Patients with acute renal failure mainly suffer from central nervous system (CNS) symptoms such as cognitive deficit, somnolence, or seizures, uremic encephalopathy in CKD has become less frequent with the use of modern techniques of renal replacement therapy. [4] Uremic polyneuropathy is a common complication of chronic renal insufficiency in the peripheral nervous system (PNS). [5-8] When patients reach the stage of chronic dialysis, a concomitant autonomic dysfunction is detectable in half of the cases. [9] In CKD; neurologists also have to consider the increased risk of drug-induced neurotoxicity. [5]

Electroencephalogram (EEG): is useful in uremic encephalopathy; it may be of diagnostic value, EEG showing generalized slowing that becomes more severe as the condition worsens. [6, 7] EEG waveforms are classified according to their frequency, amplitude, and shape. The most familiar classification uses EEG waveform frequency, following categories of frequencies are the most clinically relevant: alpha waves - 8-13 Hz, beta waves - Greater than 13 Hz, theta waves - 3.5-7.5 Hz and delta waves - 3 Hz or less. [10-12] Information about waveform frequency and shape is combined with the age of the patient to determine significance. Normal EEG waveforms are defined and described by their frequency, amplitude, and location. [13] Frequency is a key characteristic used to define normal or abnormal EEG rhythms. [14] Most waves of 8 Hz and higher frequencies are normal findings in the EEG of a child aged more than 3 years old. Waves with a frequency of 7 Hz or less often are classified as abnormal in awake adults, but they are normally seen in children or in adults who are asleep.

EEG in CKD usually shows irregular low voltage with slowing of the posterior dominant alpha rhythm and occasional theta bursts. Prolonged bursts of bilateral, synchronous slow and sharp waves or spike waves are characteristic. These changes stabilize with dialysis, provided efficient & of long duration. [15]

Patients and Methods

This study included 54 children aged (4-18 years) with different stages of chronic renal diseases (in the predialytic stage ---- stage 1 to stage 4 and dialytic stage 5). All patients were recruited from the pediatric nephrology unit and pediatric hemodialysis unit at our hospital, during the period from March 2015 to October 2016.

Epileptic children, children with abnormal CT, acute brain diseases or trauma, children with metabolic abnormalities and chronic liver diseases and children with central nervous system

infections were excluded. Children with hepatitis C also were excluded as HCV associated with neurological complications that disrupt frontostriatal structures, which may result in increased fatigue and poorer cognitive performance that may make changes in EEG study. [16]

All patients were subjected to history taking including personal history, history of chronic kidney disease and any infection, familial history of chronic kidney disease, neurological, developmental and psychogenic problems.

Full clinical examination including: General examination, local, physical examination and measurements (weight, length and body mass index (BMI).

Laboratory investigations including renal function (Serum urea, Serum creatinine), Sodium (Na), Potassium (K) and Calcium (Ca) Glomerular filtration rate (GFR) was calculated from serum creatinine by Schwartz formula. [17]

The Schwartz formula is:

$$eGFR = \frac{K \times Ht}{Cr_{\text{serum}}} \quad \text{Where, Ht = height Cr = serum creatinine}$$

K = 0.55 in children and adolescent females and k = 0.7 in adolescent males.

Sample collection: 3ml of venous blood samples were taken for, serum glucose, ALT, urea, creatinine, Sodium (Na), Potassium (K), and Calcium (Ca) levels using fully automated chemical auto-analyzer Dimension-ES, USA.

Electroencephalogram: All children were investigated by EEG. Electroencephalogram records were done using an EEG machine, flash lamp assembly, Model LS-703A/AA for electroencephalograph, NIHON-KOHDEN Corporation – JAPAN.

Electroencephalogram was recorded awake with eye closed or under sedation with chloral hydrate

For those on hemodialysis, the sample collection and EEG study were done the day after dialysis.

Statistical analysis

The numerical data were presented as means – standard deviations while nonnumerical data were presented as percentage frequency. Two tailed t-tests were used to analyze differences between the control and patients groups. P-values less than 0.05 were considered statistically significant. The magnitude of correlations was determined by Pearson's correlation coefficient. All the data were analyzed by statistical package Prism 3.0 (Graph Pad software, San Diego, CA, USA). Figures were done by Microsoft Office Excel 2007.

Results

Study sample included 54 cases with different stages of CKD; Children with CKD stage 1, 2, 3 and 4 included 24 cases & represent 24/54 i.e. 44.4% of the total sample. (6 cases for every stage (11.1%) of total sample 54 cases). Children on dialysis stage 5 were 30 cases representing 55.6% of the total sample). The mean GFR of all cases was 31.6 and the range was 5.3-100. (Figure 1). Table (1) summarize laboratory & EEG changes for total sample: The mean Urea concentration was

116.6 (mg/dl) and the mean creatinine concentration was 4.51 (mg/dl).

(Table 1) Serum electrolytes showed: mean sodium concentration was 141.1 (mEq/L), the mean potassium concentration was 5.24 (mEq/L) and the mean calcium was 0.96 (mEq/L). (Table 1) Electroencephalography findings showed, for wave form (Background): 35 cases (64.8%) had Alpha wave and 19 (35.2%) had Theta wave. (Table 1). Regarding symmetry of waves, 33 cases (61.1%) were Symmetry, 12 (22.2%) were Asymmetry, 9 cases (16.7 %) were Dysrhythmia. As regard Amplitude of waves, 18 cases (33.3%) had low amplitude, 30 cases (55.6%) had medium Amplitude and 6 cases (11.1%) had high Amplitude. (table1). For sharp wave findings, 29 cases (53.7%) had sharp wave findings and the rest 25 cases had no findings. (Table 1)

Table (2) Summaries frequency distribution of morph metric pattern of wave forms of EEG among different stages of CK with Statistical comparison between (1) early stages (1+2) Vs late (3+4) (P1) (2) Predialytic stage (mean frequency 1+2+3+4) Vs dialytic stage CKD5. Our results showed that (33.3%) of both stage 3,4 and (50%) of stage 5 shown theta record. Stage (3, 4 vs 5) had significantly (P1 <0.05) higher Theta pattern record compared to Stage 1 & 2. 50% 15 cases of Stage 5, recorded Theta pattern and showed significant high compared to

predialytic stage (p2 0.006). Sharp waves showed NS difference P1 (0.7) between 1+2 VS 3+4 with significant rise on dialysis P2 (0.0001). (Table 2)

Table (3) summarise symmetricity and amplitude of waves among different stages of CKD ,with statistical comparison between early & late predialytic stages (P1) & (2) predialytic VS dialytic stages (P2). The results showed that Stage (1,2) patients have 83.3% symmetric discharges and Stage (3,4) 41.7% with a mean for predialytic stage 62.5% & stage (5) showed 60 % symmetric discharge, P1 (0.01) & P2 (0.8). Regarding the distribution of amplitude of waves among different CKD stages. For low Amplitude (<50 uV), there were no cases in stage (1 & 2) however, 1 case (16.7%) in stage (3), 3 cases (50.0%) in stage 4 and 14 cases (46.7%) in stage 5. 1+2 VS 3+4 showed P1 (0.01) Whereas predialytic VS dialytic showed P2 (0.02). For medium Amplitude, there were 10 cases (83.3%) in stage (1 +2), 8 cases (66.7%) in stage 3+4 (P1 0.2) and there was a significant higher prominence of medium amplitude in predialytic stage compared to dialytic stage (p 0.01). (Table 3). The results revealed that there was a significant higher prominence in low and medium amplitude in stage 4 and 5 and as the disease progresses low amplitude predominates. (Figure 2)

Table 1 Laboratory and Electroencephalography findings of the studied group 54 cases.

Variable		Description (54 cases)
Urea(mg/dl)		116.6 ± 73.1 (16-226)
Creatinine(mg/dl)		4.51 ± 3.16 (0.50-10.9)
Sodium(mEq/L)		141.1 ± 7.7 (130-156)
Potassium(mEq/L)		5.24 ± 1.52 (2.40-8.90)
Calcium(mEq/L)		0.96 ± 0.13 (0.80-1.20)
Wave form (Background)	Alpha	35 (64.8%)
	Theta	19 (35.2%)
Symmetry of waves	Symmetry	33 (61.1%)
	Asymmetry	12 (22.2%)
	Dysrhythmia	9 (16.7%)
Amplitude of waves	Low	18 (33.3%)
	Medium	30 (55.6%)
	High	6 (11.1%)
Sharp wave findings	No	25 (46.3%)
	Yes	29 (53.7%)

Table 2 Distribution of Morphometric pattern of wave forms of EEG among different CKD stages % Frequency (1) between early stages 1+2 vs 3+4 (2) predialytic stage mean frequency versus dialytic stage.

Wave form	CKD stages						P. value	
	Stage (1) (n = 6)	Stage (2) (n = 6)	Stage (3) (n = 6)	Stage (4) (n = 6)	Predialytic (24)	Stage (5) (n = 30)	P1	P2
Alpha	6 (100.0%)	6 (100.0%)	4 (66.7%)	4 (66.7%)	20 (83.3%)	15 (50.0%)	0.03*	0.005*
	12 (100%)		8 (66.7%)					
Theta	0	0	2 (33.3%)	2 (33.3%)	4 (16.7%)	15 (50.0%)	0.03*	0.006*
	0		4 (33.3%)					
Sharp waves	3 (50.0%)	1 (16.7%)	1 (16.7%)	2 (33.3%)	7 (29.2%)	22 (73.3%)	0.7	0.0001*
	4 (33.3%)		3(25%)					

Table 3 Comparison for EEG findings symmetry & amplitude: between (1) early stage CKD 1+2 versus CKD 3+4 (2) predialytic stage VS dialytic stage.

	CKD stages						P. value	
	Stage (1) (n = 6)	Stage (2) (n = 6)	Stage (3) (n = 6)	Stage (4) (n = 6)	Predialytic (24)	Stage (5) (n = 30)	P1	P2
Symmetry	6 (100.0%)	4 (66.7%)	2 (33.3%)	3 (50.0%)	15 (62.5%)	18 (60.0%)	0.01*	0.8
	10 (83.3%)		5 (41.7%)					
Asymmetry	0	1 (16.7%)	2 (33.3%)	3 (50.0%)	6 (25%)	6 (20.0%)	0.2	0.7
	1 (8.3%)		5 (41.7%)					
Dysrhythmia	0	1 (16.7%)	2 (33.3%)	0	3 (12.5%)	6 (20.0%)	0.1	0.5
	1 (8.3%)		2 (16.7%)					
Low	0	0	1 (16.7%)	3 (50.0%)	4 (16.7%)	14 (46.7%)	0.01*	0.02*
	0		4 (33.3%)					
Medium	6 (100.0%)	4 (66.7%)	5 (83.3%)	3 (50.0%)	18 (75%)	12 (40.0%)	0.2	0.01*
	10 (83.3%)		8 (66.7%)					
High	0	2 (33.3%)	0	0	2 (8.3%)	4 (13.3%)	0.1	0.6
	2 (16.7%)		0					

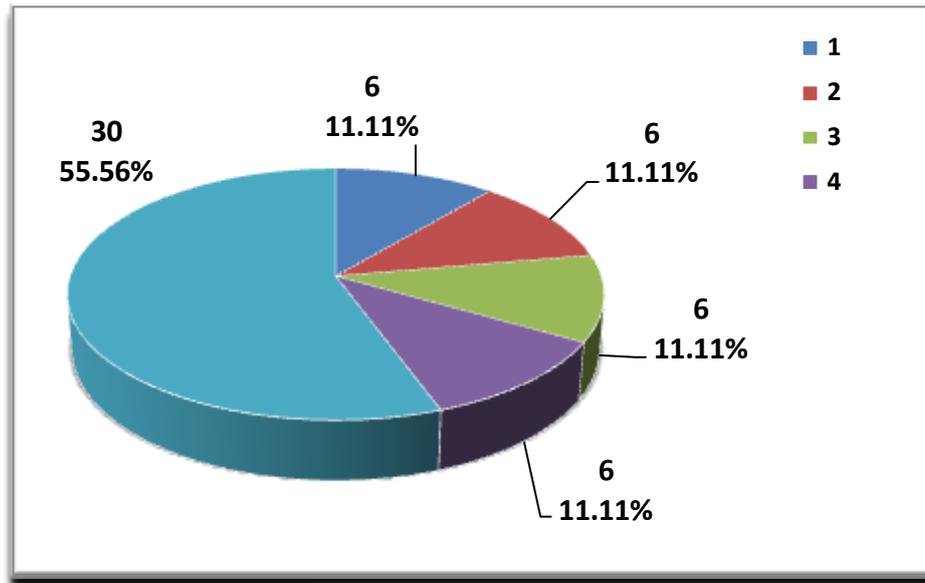


Figure 1 Stages of chronic kidney disease and GFR of the studied group

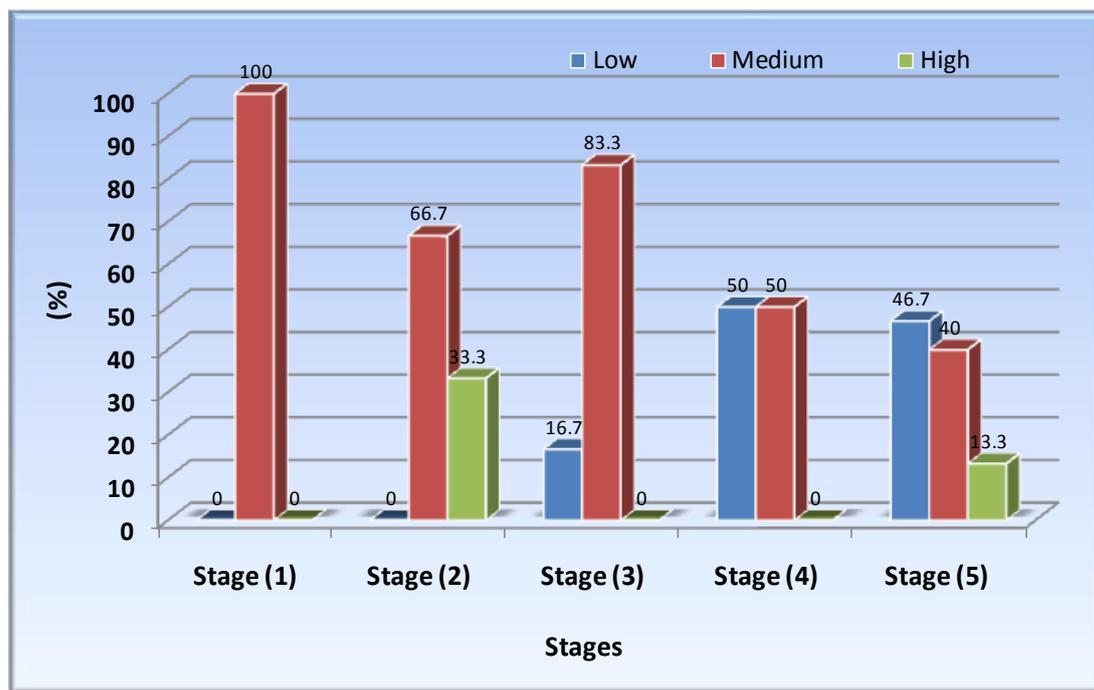


Figure 2 Distribution of Amplitude of waves among different CKD stages.

Discussion

In this prospective observational study, we included 54 children (22 males and 32 females) with different stages of chronic renal diseases with mean age of 12.2 years ranged (4-18). Regarding electroencephalography findings, for wave form (Background), 35 cases (64.8%) had Alpha wave and 19 (35.2%) had Theta wave. Regarding symmetry of waves, 33 cases (61.1%) were Symmetry, 12 (22.2%) were Asymmetry, 9 cases (16.7 %) were dysrhythmia this was similar to results of Murray DM et al., [18] As regard Amplitude of waves, 18 cases (33.3%) had low amplitude, 30 cases (55.6%) had medium Amplitude and 6 cases (11.1%) had high Amplitude. For Sharp wave findings, 29 cases (53.7%) had sharp wave findings and the rest 25 cases had no findings this was similar to results of Kurella TM.,etal.. [19]

Regarding the distribution of Morphometric pattern of wave forms of EEG among different CKD stages, all patients were awake during the EEG recording and it is evident that alpha activity remained predominantly in the entire stages of CKD this also was described in the study of Krishnan AV. & Kiernan MC. [20]

Our present results revealed that stages (3, 4 & 5) had significantly higher Theta pattern record compared to stages 1 & 2. (33.3% of both stage 3 & 4 and 50% of stage 5 cases have shown theta records). The present results are in agreements with those of Gadewar et al., [15] who studied electroencephalogram changes in 83 patients in different stages of chronic kidney disease. They found that Theta pattern record was significantly higher in Stage 4 and 5 compared to other CKD stages. These results are in agreement with Demir et al., [21] who studied EEG changes in 44 patients diagnosed as uremic encephalopathy and found decreased alpha activity in 8.5% (n=26) and generalized asynchronous slow wave activity in 5.2% (n=16).

In 2016, Lai et al., [22] studied neurologic disorders in 74 patients affected by CKD and the results showed significant differences in the absolute and relative power of delta band and relative power of theta band of EEG ($p=0.008$, $p<0.001$, $p=0.051$) respectively. Also, Röhl et al., [23] found out that electrical power was most prominent in delta, theta and alpha frequencies in the temporal and central brain areas. It was reported by Arieff et al., [24] that EEG abnormalities in uremic encephalopathy is reflected through appearance of theta waves, disappearance of normal basic rhythms and diminished reactivity of EEG to afferent stimulation and domination by generalized delta activity. All these changes are mostly appreciated in the frontal leads. Arnold and Krishnan, [25] reported that the typical features of an EEG in uremic neuropathy are often non-specific such as a slowing of the alpha rhythm with excess delta and theta waves.

In the current study, results indicated that stage 1 CKD patients have symmetric discharges and stage (3, 4 & 5) had significantly higher asymmetry pattern and dysrhythmia pattern records compared to Stage 1 & 2 (20.0% of stage 5 cases had asymmetry pattern and also, 20.0% of stage 5 cases had dysrhythmia pattern). These findings were in agreement with Gadewar et al., [15] who found that as the stage of CKD progresses both asymmetry and dysrhythmia tend to increase (12.5% to 50 % for asymmetry and 12.5% to 34.62% for dysrhythmia) with a significant difference. The results of this study revealed that there is a significant increase of low

amplitude (<50 uV) in stage 4 (50.0%) and stage 5 (46.7 %) respectively compared to stage 1 & 2. These results are in line with those of Gadewar et al., [15] who found that low amplitude had significantly high prevalence in patients of 4 and 5 CKD stages. Similarly, Koçer et al., [26] also found out that in the early stages of uremia, EEG recordings were generally normal but as the disease progressed low amplitude waves predominate. Chen et al., [27] studied changes of EEG in dialysis encephalopathy and reported that EEG findings consist of abundance of low waves.

The results of the present study demonstrated that with the progression of CKD stage, sharp wave transients or findings increases (stage 5 had sharp wave transients in 22 cases, 73.3%) with a significant difference compared to the earlier CKD stages. Also, Gadewar et al., [15] found that frontal and fronto – temporal sharp wave transients were noted as the stage progressed and were prominently present in stage 5 and stage 4, frontal sharp wave transients 50% in stage 5 and 71.43% in stage 4 and temporo frontal sharp wave transients 50 % in stage 5 and 14.29% in stage 4. Also, Koçer et al., [26] found sharp wave transients in the later stages of CKD, occipital sharp wave transients is noted in stage 4 and p-value is found to be significant in the distributional pattern at different progressive stages of CKD. Demir et al. [21] found bilateral spike wave activity in 14% of the patients with uremic encephalopathy who clinically don't have seizures and in 20% triphasic waves can be encountered in direct proportion of blood urea level. Arnold and Krishnan, [25] added that triphasic sharp waves on EEG are considered a specific feature of metabolic encephalopathy.

Conclusion

We concluded that pediatric patients with chronic kidney disease have distinct EEG deviations from normality and EEG can be used as a prognostic indicator of response to clinical therapy of CKD.

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Statements

Ethics approval and consent to participate

This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Helsinki and agreed by the faculty of medicine, Minia university, Ethical committee (No: 116-11-2014) and informed written consent was obtained in every case from their legal guardians.

Consent for publication

“Not applicable”

Availability of data and material

“Not applicable”

Conflict of interest

The authors declare no conflict of interest.

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