The Egyptian Journal of Hospital Medicine (October 2022) Vol. 89 (2), Page 7248- 7254

Assessment of Electroencephalographic Changes in Different Stages of Chronic Kidney Disease

Sabry Abdel Rahman Tolba, Ali M. Abu Zeid, Mohamed A. Arafa, Mohammed A. Abdel Kawy*
Department of Pediatrics, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Mohammed A. Abdel Kawy, **Mobile:** (+20) 01090654982, **Email:** ahamad198718@gmail.com

ABSTRACT

Background: Chronic Kidney Disease (CKD) is defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) working group of the National Kidney Foundation (NKF) as evidence of structural or functional kidney abnormalities that persist for at least 3 months, with or without a decreased Glomerular Filtration Rate (GFR). Electroencephalogram (EEG) is useful in assessing patients in uremic encephalopathy and in monitoring their progress.

Objective: The aim of the current study was ro evaluate the EEG changes in different stages of CKD.

Patients and methods: This cross-sectional study was conducted in the Pediatrics Department at Zagazig University Hospitals on 61 patients with CKD at different stages. All included patients had been subjected to predesigned working sheet. Serum creatinine level, 24-hour urinary protein excretion, estimation of glomerular filtration rate and EEG were done for all patients. GFR was calculated by MDRD formula.

Results: Our study showed statistically significant increased asymmetry and dysrhythmia among stages 3 and 4 than stages 1 and 2, while symmetry was statistically significant higher among stages 1 and 2 than stages 3 and 4. There was statistically significant increased low amplitude among stages 3 and 4 than stages 1 and 2, while high amplitude was higher among stages 1 and 2 than stages 3 and 4, with no significant difference between the pre-dialytic stages regarding medium and high amplitudes. There was highly statistically significant difference between the CKD patients with and without neuropathy regarding albumin, creatinine and eGFR where albumin and creatinine was higher among uremic neuropathy patients than non-uremic neuropathy, while eGFR was highly significantly higher among the non-uremic neuropathy than the uremic neuropathy patients.

Conclusion: EEG findings which are characteristics of uremic encephalopathy can be present in CKD patients without frank signs of encephalopathy**.**

Keywords: Chronic Kidney Disease, Electroencephalographic Changes, Uremic encephalopathy.

INTRODUCTION

Chronic kidney disease (CKD) is caused by a variety of diverse disease processes that, over the course of months or years, irreversibly affect the structure and function of the kidney. The presence of structural kidney damage and a persistent decline in renal function are necessary for the diagnosis of CKD. Glomerular filtration rate (GFR) is the greatest indication of total renal function currently available [(1)].

By placing electrodes on the scalp, the Electroencephalogram (EEG) records the electrical activity of the brain. When it comes to diagnosing tumors, strokes, and other localized brain illnesses, EEG was formerly the first line of defense, but high-resolution anatomical imaging methods like magnetic resonance imaging (MRI) and computed tomography (CT) have replaced it [(2)].

Electroencephalography in chronic renal failure shows general EEG slowing, particularly slowing of the alpha rhythm in the early stages of renal illness, with a more pronounced downward shift in the main frequency from alpha toward theta as renal failure advances [(3)].

EEG study in various phases of CKD were conducted by **Gadewar *et al.*[(4)]** they came to the conclusion that EEG is a useful method for detecting latent or subclinical uremic encephalopathy. Patients with CKD may have EEG results that are indicative of uremic encephalopathy even in the absence of overt encephalopathy symptoms. EEG can therefore be utilized as a predictive predictor of CKD clinical therapeutic response. This study was carried out to assess the EEG alterations in various phases of CKD.

PATIENTS AND METHODS

This cross-sectional study was conducted in the Pediatrics Department at Zagazig University Hospitals on 61 patients with CKD at different stages.

Inclusion criteria:

(1) Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, indicated by one or more the following: abnormalities by kidney biopsy, abnormalities based on imaging tests and abnormalities in the composition of the blood or urine.

(2) GFR <60 ml/minute/1.73 m^2 for ≥3 months, with or without the signs of kidney damage.

Exclusion criteria:

- Patients with chronic kidney disease who did not perform renal biopsies.
- Patients with history of stroke, epilepsy, dementia, metabolic abnormalities, chronic liver diseases or COAD.

Received: 15/07/2022
Accepted: 18/09/2022

METHODS

- Personal and sociodemographic data.
- Family history.
- Medical history.
- General examination e.g. vital signs, mental status and general look (pallor, cyanosis).
- Local examination e.g. cardiac examination, chest examination, abdomen examination, and neurological examination.
- Serum creatinine level, 24-hour urinary protein excretion and estimation of glomerular filtration rate for all patients. GFR was calculated by MDRD formula.
- EEG was done for all patients. The EEG tracing was analyzed as regards: background activity, generalized slowing or spike wave, focal slowing or spike wave, polyspike and focal with secondary generalization.

Classification of disease severity:

All cases were classified as per the 'The Kidney Disease Outcomes Quality Initiative' (K/DOQI) of the National Kidney Foundation (NKF) classification of 2002. Accordingly, all cases were classified on initial evaluation as: Stage I, Stage II, Stage III, Stage IV and Stage V.

Ethical Consideration:

An approval of the study was obtained from Zagazig University Faculty of Medicine Academic and Ethical Committee (IRB code number (MS.20.03.1090). Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data collected and encoded using Microsoft Excel software. Data were then imported into Statistical Package for Social Sciences (SPSS version 23) software for analysis.

According to the type of data, qualitative represented as numbers and percentages, while quantitative data represented by mean and standard deviation (SD). Chi-square test ($\chi 2$) and Fisher's exact test to calculate difference between two or more groups of qualitative variables. Independent samples t-test was used to compare between two independent groups of normally distributed variables. Receiver operating characteristics (ROC) curve is used for predicting the diagnostic ability of quantitative variables. P-value was set at ≤ 0.05 for significant results, and ≤ 0.001 for highly significant results.

RESULTS

The average age of the studied group was 70.6 (SD 6.9) months and ranged from 7 months to 18 years. Regarding sex, 57.4% were males and 42.6% were females **(Table 1)**.

Table (1): Socio-demographic characteristics of the studied group.

Demographic data		**The studied group (n=61)**
		Mean ± SD Median (Range)
Age (months)		**70.6±6.9 65.5 (7 months -18 years)**
Age grouping	Less than 1 year 1-5 years 5-10 years 10-15 years ≥15 years	17 (27.8%) 13 (21.3%) 7 (11.5%) 15 (24.6%) 9 (14.8%)
Gender N (%)	Male Female	35 (57.4%) 26 (42.6%)

About the 46% of the studied group were pre-dialytic divided equally 7 patients in each stage of CKD and 54% of them were dialytic **(Figure 1)**. A total of 39 patients (63.9%) had alpha wave form, medium amplitude was the commonest (49.2%), most of the studied group (60.7%) had symmetric waves and 45.9% had sharp wave findings **(Figure 2)**.

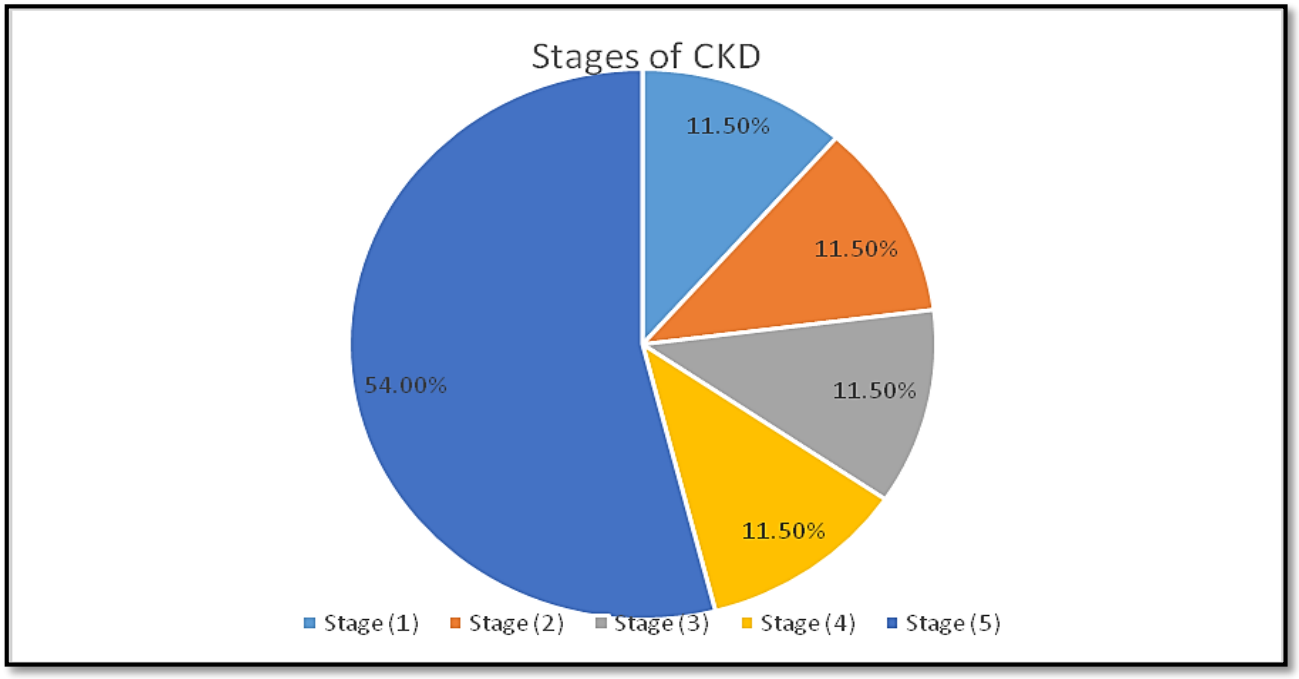

Figure (1): Pie chart for stages of CKD among the studied group.

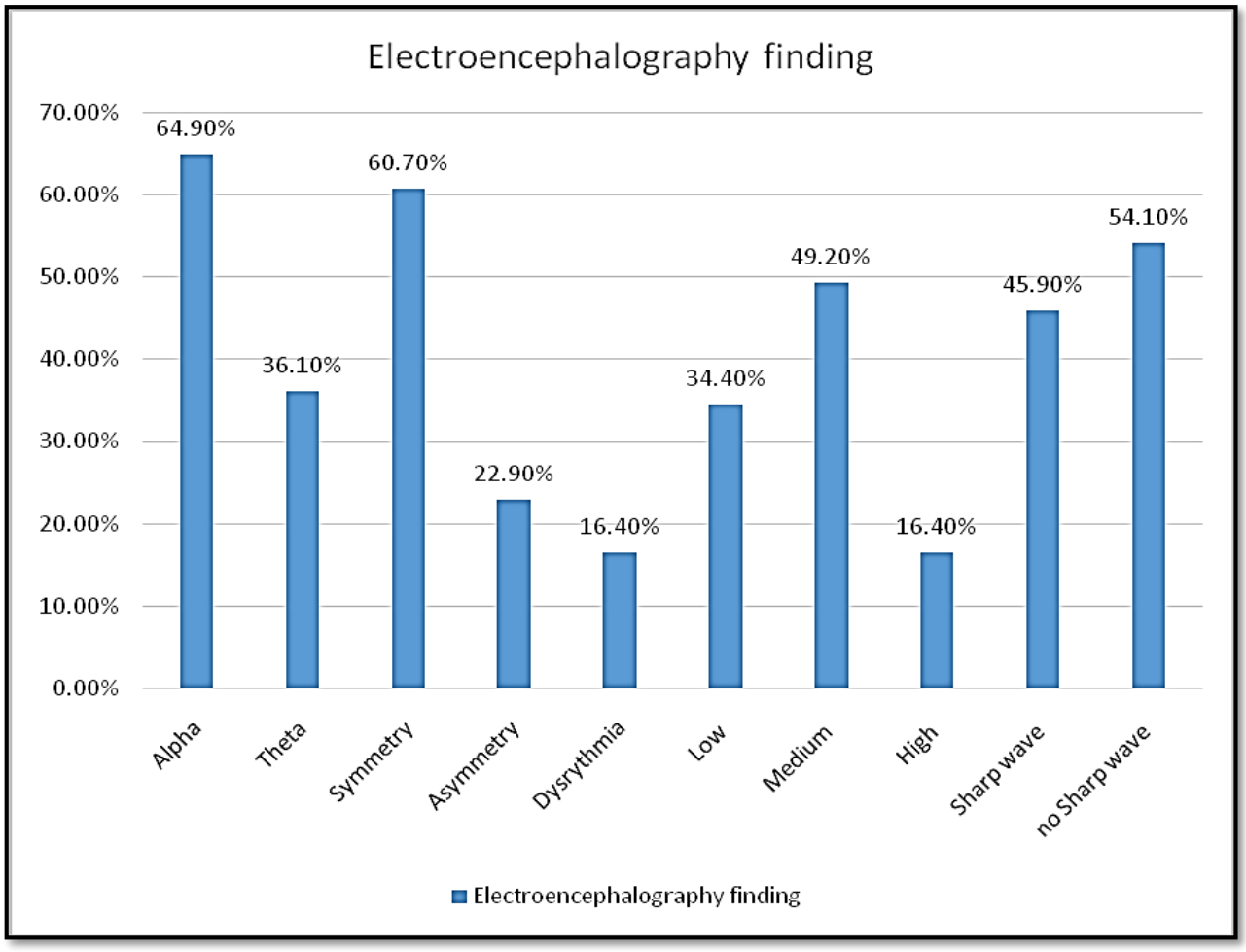

Figure (2): Bar chart for Electroencephalography findings among the studied group.

There was statistically significant increased alpha wave among stage 1 and 2 than stage 3 and 4 while theta was statistically significant higher among stage 3 and 4 than stage 1 and 2. Regarding sharp waves, there was no significant difference between the predialytic stages **(Table**

Table (2): Distribution of morphometric pattern of wave forms of EEG among the pre-dialytic stages of CKD patients.

Wave form	Pre-dialytic CKD stages				χ^2	P-value
	Stage (1) No=7 (%)	Stage (2) No=7 (%)	Stage (3) No=7 (%)	Stage (4) No=7 (%)		
Alpha	7 (100%)	7 (100%)	5 (71.4%)	5 (71.4%)	4.7	**0.04***
	14 (100%)		10 (71.4%)			
Theta	0 (0.0%)	0 (0.0%)	2 (28.6%)	2 (28.6%)		
	0 (0.0%)		4 (28.6%)			
Sharp waves	4 (57.1%)	2 (28.6%)	1 (14.3%)	2 (28.6%)	0.19	0.6
	6 (42.8%)		3 (21.4%)			

*Statistically significant difference (≤0.05).

There was statistically significant difference between the pre-dialytic and dialytic stages of CKD patients regarding morphometric pattern of waveforms where most of the pre-dialytic (85.7%) had alpha wave while most of the dialytic (54.6%) had theta wave. Regarding sharp waves, they were highly significantly higher among the dialyticthan the predialytic stages **(Table 3)**.

Table (3): Distribution of morphometric pattern of waveforms of EEG among the pre-dialytic and dialytic stages of CKD patients.

Wave form	CKD stages		χ^2	P-value
	The pre-dialytic stage No=28(%)	The dialytic stage No=33(%)		
Alpha	24 (85.7%)	15 (45.4%)	12.3	0.001**
Theta	4 (14.3%)	18 (54.6%)		
Sharp waves	9 (32.1%)	19 (57.6%)	10.1	0.001**

**Statistically highly significant difference (<0.001)

There was statistically significant increased asymmetry and dysrhythmia among stages 3 and 4 than stages 1 and 2 while symmetry was statistically significant higher among stages 1 and 2 than stages 3 and 4 **(Table 4)**.

Table (4): Relation between EEG findings symetricity and the pre-dialytic stages of CKD patients.

EEG symetricity	Pre-dialytic CKD stages				χ^2	P-value
	Stage (1) No=7 (%)	Stage (2) No=7 (%)	Stage (3) No=7 (%)	Stage (4) No=7 (%)		
Symmetry	7 (100%)	5 (71.4%)	2 (28.6%)	3 (42.8%)	7.7	0.02*
	12 (85.7%)		5 (71.4%)			
Asymmetry	0 (0.0%)	1 (14.3%)	3 (42.9%)	4 (57.1%)		
	1 (7.1%)		7 (50.0%)			
Dysrhythmia	0 (0.0%)	1 (14.3%)	2 (28.6%)	0 (0.0%)		
	1 (7.1%)		2 (14.3%)			

*Statistically significant difference (≤0.05)

There was statistically significant increased low amplitude among stages 3 and 4 than stages 1 and 2, while high amplitude was higher among stages 1 and 2 than stages 3 and 4 with no significant difference between the pre-dialytic stages regarding medium and high amplitudes **(Table 5)**.

Table (5): Frequency of EEG amplitudes among the pre-dialytic stages of CKD patients.

EEG amplitudes	Pre-dialytic CKD stages				χ^2	P-value
	Stage (1) No=7 (%)	Stage (2) No=7 (%)	Stage (3) No=7 (%)	Stage (4) No=7 (%)		
Low	0 (0.0%)	0 (0.0%)	2 (28.6%)	4 (57.2%)	7.6	0.002*
	0 (0.0%)		6 (42.8%)			
Medium	7 (100%)	4 (57.2%)	5 (71.4%)	3 (42.8%)	1.4	0.1
	11 (78.6%)		8 (57.2%)			
High	0 (0.0%)	3 (42.8%)	0 (0.0%)	0 (0.0%)	1.5	0.1
	3 (42.8%)		0 (0.0%)			

*Statistically significant difference (≤0.05)

There was statistically significant difference between the pre-dialytic and dialytic stages of CKD patients regarding EEG amplitudes where more than half of the dialytic (45.5%) had low amplitude while most of the pre-dialytic (67.9%) had medium amplitude **(Table 6)**.

Table (6): Comparing EEG amplitudes among the pre-dialytic and dialytic stages of CKD patients

EEG amplitudes	CKD stages		χ^2	P-value
	The pre-dialytic stage No=28(%)	The dialytic stage No=33(%)		
Low	6 (21.4%)	15 (45.5%)	7.2	0.02*
Medium	19 (67.9%)	11 (33.3%)		
High	3 (10.7%)	7 (21.2%)		

*Statistically significant difference (≤0.05).

There was highly statistically significant difference between the CKD patients with and without neuropathy regarding albumin, creatinine and eGFR where albumin and creatinine was higher among uremic neuropathy patients than non-uremic neuropathy while eGFR, it was highly significantly higher among the non-uremic neuropathy than the uremic neuropathy patients **(Table 7)**.

Table (7): Comparing albumin, creatinine and eGFR among the CKD patients with and without neuropathy

Kidney functions	CKD with neuropathy No=13 (%)	CKD without neuropathy No=48 (%)	T-test	P-value
Albumin (gm/dl) Mean ± SD	4.91 ± 0.36	4.05 ± 0.23	10.5	<0.001**
eGFR (ml/min/1.73m2) Mean ± SD	17.51 ± 4.3	24.9 ± 1.5	8.3	<0.001**
Creatinine (mg/dl) Mean ± SD	8.5 ± 0.73	6.14 ± 0.52	13.2	<0.001**

**Statistically highly significant difference (<0.001)

DISCUSSION

CKD affects people all over the world. In the latter stages of CKD, uremic symptoms manifest clearly. Global cerebral dysfunction known as encephalopathy, which can potentially result in lifelong brain damage, frequently occurs in the absence of main structural brain illness. The symptoms frequently start slowly and go unnoticed by the patients, only becoming apparent to their family members or caretakers [5,6].

Clinical uremic encephalopathy, a condition caused by renal failure, is characterized by a variety of symptoms, including mental drowsiness, lowered mental acuity and vigilance, drowsiness, stupor, coma, irritability, restlessness, myoclonus, seizures, anorexia, nausea, vomiting, itching, and hypothermia [7].

EEG is helpful in evaluating and tracking the development of individuals with uremic encephalopathy. The correlation between EEG results and clinical symptoms suggests that they may have diagnostic significance. Additionally, it may be helpful to rule out additional sources of uncertainty, such as infections or structural issues [5,8].

Our study evaluated the EEG changes in different stages of CKD. This cross-sectional study was conducted in the Pediatrics Department at Zagazig University Hospitals on 61 patients with CKD at different stages.

All included patients had been subjected to predesigned working sheet including personal and sociodemographic data, family history, medical history and clinical examination. Serum creatinine level, 24-hour urinary protein excretion and estimation of GFR rate were done for all patients. GFR was calculated by MDRD formula. EEG was done for all patients.

Our study showed that the average age of the studied group was 70.6 (SD 6.9) months, 27.8% were less than one year and 24.6% was from 10 to 15 years. Regarding sex, 57.4% were males and 42.6% were females. **Gadewar *et al.*** [4] studied EEG in different stages of CKD. They enrolled 83 patients in different stages of CKD. The age ranged from 17 to 80 years. Of these, maximum patients were in age group 61-70 (24.1%). Mean age of the patients enrolled for EEG was 50.5 (SD 15.5) years.

Our study showed that 46% of the studied group were pre-dialytic divided equally 7 patients in each stage of CKD and 54% of them were dialytic. **Gadewar *et al.*** [4] found that one third patients were in stage V (31.3%), stage IV and stage III consists of (16.9%) and (18.1%) respectively. Less patients were seen in stage I (14.5%) suggesting there is a delayed diagnosis of CKD on onset.

Our study showed that 39 (63.9%) patients had Alpha wave form, medium amplitude was the commonest (49.2%), most of the studied group (60.7%) had symmetric waves and (45.9%) had sharp wave findings.

Bansal Manoj [9] found that the severity of the abnormal EEG changes correlated well with the severity of the clinical features and with the renal damage.

We found statistically significant increased alpha wave among stages 1 and 2 than stages 3 and 4 while theta was statistically significant higher among stages 3 and 4 than stages 1 and 2. Regarding sharp waves, there was no significant difference between the predialytic stages. Also, there was statistically significant difference between the pre-dialytic and dialytic stages of CKD patients regarding morphometric pattern of waveforms, where most of the pre-dialytic (85.7%) had alpha wave, while most of the dialytic (54.6%) had theta wave. Regarding sharp waves, they were highly significantly higher among the dialytic than the predialytic stages.

Gadewar *et al.* [4] showed the pattern of dispersion of sharp waves transients in the various stages of CKD. They noticed a relative predominance of centro-frontal sharp wave transients in an awake recording in stage II (50%) and stage III (33.33%) and isolated centro-temporal sharp wave transients in stage III (33.33%) and parieto-occipital sharp wave transients simulated the centro frontal pattern in CKD. Interestingly, frontal and fronto – temporal sharp wave transients were noted as the stage progressed and were prominently present in stage IV and stage V, frontal sharp wave transients 50% in stage IV and 71.43% in stage V and temporo-frontal sharp wave transients 50 % in stage IV and 14.29% in stage V.

Gadewar *et al.* [4] illustrated distribution of morphometric EEG pattern with relation to different stages of CKD. Almost all patients were awake during the EEG recording and it is evident that alpha activity has remained predominantly in the entire stages of CKD. However, in addition to alpha pattern stage II, stage IV and stage V have shown a significant decrease in beta activity 25%, 21.43% and 15.38% respectively. It was also documented that 14.29% of stage IV and 15.38 % of patients of stage V have shown theta and beta records both. Usually, theta and beta records are reflection of excitatory post-synaptic cumulative neuronal transmission which suggests that firing rate in stage IV and stage V increases to certain extent. Also, there is progressive increase in the change of alpha wave on afferent stimulation as the CKD stages progress.

Interestingly, 14.29%, 11.54% of stage 5 patients have demonstrated generalized delta activity and they were found to be significant **($p<0.0001$)**.

Our study showed statistically significant increased asymmetry and dysrhythmia among stages 3 and 4 than stages 1 and 2, while symmetry was statistically significant higher among stages 1 and 2 than stages 3 and 4.

However, there was no statistically significant difference between the pre-dialytic and dialytic stages of CKD patients regarding EEG findings symmetricity. **Gadewar *et al.*** [4] confirmed that in Stage I patients

have typically symmetric discharges. The evidence of asymmetry and dysrhythmia were noted from stage II onwards. As the stage of CKD progresses both asymmetricity and dysrhythmia tend to consolidate 12.5% to 50 % for asymmetricity and 12.5% to 34.62% for dysrhythmia and they were found to be significant **(p<0.0001)**.

Our study showed that there was statistically significant increased low amplitude among stages 3 and 4 than stages 1 and 2, while high amplitude was higher among stages 1 and 2 than stages 3 and 4 with no significant difference between the pre-dialytic stages regarding medium and high amplitudes. Also, there was statistically significant difference between the pre-dialytic and dialytic stages of CKD patients regarding EEG amplitudes where more than half of the dialytic (45.5%) had low amplitude while most of the pre-dialytic (67.9%) had medium amplitude.

Gadewar *et al.* [4] showed progressively disappearing high amplitude (>150 uV), whereas there is a sudden surge of low amplitude (<50 uV) in stage IV (57.14%) and stage V (57.69%) respectively. There are equivocal reflections in medium amplitude, however, both low amplitude and high amplitude pattern of EEG have found to be significant **(p< 0.0001)** as the stage progresses.

Our study showed that there was highly statistically significant difference between the CKD patients with and without neuropathy regarding albumin, creatinine and eGFR where albumin and creatinine was higher among uremic neuropathy patients than non-uremic neuropathy, while eGFR was highly significantly higher among the non-uremic neuropathy than the uremic neuropathy patients.

Therefore, albumin, eGFR and creatinine were reliable markers for detection of neuropathy among CKD patients with 100% sensitivity and 95%, 100% and 98% accuracy, respectively.

Teschan *et al.* [10] concluded that pathologic EEG changes correlates with creatinine levels.

Very few data are available regarding EEG changes in CKD. **Bansal Manoj** [9] found out that with increasing severity there is increase in the slow wave activity

Gadewar *et al.* [4] found that EEG can be used as an effective tool for detection of subclinical or latent uremic encephalopathy. EEG findings which are characteristics of uremic encephalopathy can be present in CKD patients without overt signs of encephalopathy. So, EEG can be used as a prognostic indicator of response to clinical therapy of CKD.

CONCLUSION

Uremic encephalopathy is a known complication of CKD. EEG is an effective tool for diagnosis of uremic encephalopathy. Interestingly, EEG can be used as an effective tool for detection of subclinical or latent uremic encephalopathy, where patients do not show any overt clinical signs of uremic encephalopathy.

EEG findings which are characteristics of uremic encephalopathy can be present in CKD patients without frank signs of encephalopathy, suggesting that the neurologic electrophysiological abnormality persists whether or not the patients shows any overt signs of uremic encephalopathy.

- **Conflict of interest:** The authors declare no conflict of interest.
- **Sources of funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
- **Author contribution:** Authors contributed equally in the study.

REFERENCES

1. **Levey A, Becker C, Inker L (2015):** Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA., 313:837-46.
2. **Tatum W (2014):** Ellen R. Grass Lecture: Extraordinary EEG. Neurodiagnostic Journal, 54(1):3-21.
3. **Pickett J, Theberge D, Brown W (1999):** Normalizing hematocrit in dialysis patients improves brain function. Am J Kidney Dis., 33:1122-30.
4. **Gadewar P, Acharya S, Khairkar P (2015):** Dyanmics of Electroencephalogram (EEG) in different stages of chronic kidney disease. Journal of Clinical and Diagnostic Research, 9(3): 25-C27.
5. **Van Dijck A, Van Daele W, De Deyn P (2012):** Uremic Encephalopathy, Miscellanea on Encephalopathies: A Second Look, Dr. Radu Tanasescu (Ed.).DOI: 10.5772/33452
6. **Inker L, Astor B, Fox C *et al.* (2014):** KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis., 63(5):713-35.
7. **Teschan P, Ginn H, Bourne J (2015):** Quantitative indices of clinical uremia. Kidney Int., 15(6):676-97.
8. **Cohlan S (2002):** K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis., 39(2):1-246.
9. **Bansal Manoj K (2009):** EEG Changes In Uraemic Encephalopathy. Journal of Community Medicine, 5(1):15-8.
10. **Teschan P, Bourne J, Reed R (1983):** Electrophysiological and neurobehavioral responses to therapy: The National Cooperative Dialysis Study. Kidney International. Kidney Int., 13:58-65.