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Research Article

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Uremic Seizures with Chronic Kidney Disease: Clinical Types, Possible Mechanisms and Response to Treatments

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Abstract

Background and objectives: Recurrent seizures are a consequence of uremia due to chronic kidney disease (CKD). This study was aimed to determine types, frequencies, causes and treatments of uremic seizures and their independent predictors.

Methods: Seventy adults (male = 33; female = 37) were included. They had mean age of 45.87 ± 3.36 years and duration of kidney failure (stage 3-5) of 5.53 ± 1.53 years. They underwent clinical and laboratory investigations and electroencephalography (EEG) and brain neuroimaging.

Results: Eleven patients (15.7%; on dialysis = 6, not on dialysis = 5) developed recurrent seizures after the development of CKD. Six had (54.55%) generalized tonic-clonic (GTC) seizures, of them 4 (66.67%) had tetany, hypocalcemia (< 6 mg/dl), hyperparathyroidism and brain calcifications. Five (45.45%) had focal to bilateral GTC seizures, focal electroencephalography (EEG) epileptic discharges and white matter ischemic hyperintensities in their brain magnetic resonance imaging. Epileptic EEG discharges (spikes and spike-wave complexes) were found in 24.3% (n = 17) in absence of seizures. Compared to those without seizures, the majority of patients with seizures had end stage kidney disease (ESKD), metabolic derangements and neuroimaging abnormalities. Multiple regression analysis showed that the presence of uremic seizures was independently correlated to the severity of kidney failure (OR = 1.25, 95% Cl = 1.08-1.30, P = 0.01) and metabolic derangements (OR = 2.44; 95% CI = 1.25-2.80, P = 0.01).

Conclusion: Recurrent seizures are common with uremia. The progression of uremia and its acute manifestations (as uremic encephalopathy with/of without metabolic derangements) were the most common precipitating factors for uremic seizures. Improvements of seizures occurred with hemodialysis and correction of metabolic derangements.

Keywords

Chronic kidney disease (CKD), Uremia, Seizures

Abbreviations

CKD: Chronic Kidney Disease; **ESKD:** End Stage Kidney Disease; **CNS:** Central Nervous System; **GTC:** Generalized Tonic-Clonic; **EEG:** Electroencephalography; **MRI:** Magnetic Resonance Imaging; **WMH's:** White Matter Ischemic Hyperintensities; **AEDs:** Antiepileptic Drugs

Introduction

Uremic syndrome of chronic kidney disease (CKD) is a common health problem with an estimated prevalence of 13-35% [1]. The most common worldwide causes of CKD are diabetes mellitus and nephritis [2]. Central, peripheral and autonomic nervous system dysfunctions are common consequences of uremic syndrome of CKD and contribute to patients' morbidity and mortality [3]. Recurrent seizures (myoclonic, generalized tonic-clonic or GTC and focal) are common central nervous system (CNS) complications of uremia. They may occur as a manifestation of acute metabolic derangements such as hypocalcemia, hyperphosphatemia, hypomagnesemia and hyperkalemia, acidosis [4, 5], hypertensive encephalopathy [6], brain edema [7] and renal hyperparathyroidism [5, 8], which also contribute to the occurrence of uremic encephalopathy in end stage kidney disease (ESKD) or in earlier stages of kidney failure due to CKD [4, 9].

Experimental and clinical studies confirmed multifactorial mechanisms of recurrent seizures with uremia, they include accumulation of endogenous (e.g. guanidine compounds) and exogenous toxins, oxidative stress, and apoptosis [4, 9] and brain angiopathies [3, 10-12]. Neuroimaging studies of patients with uremic seizures reported white matter ischemic hyperintense lesions (WMH's) [3, 11, 12], cerebral hemispheric, basal ganglionic, thalamic and brainstem ischemic infarctions; brain hemorrhage [10]; cortical and subcortical brain edema [7]; and brain calcifications [3, 8]. The main lines of treatment of uremic seizures are proper treatment of the cause of CKD and its comorbid medical diseases, optimizing renal replacement therapy and correction of associated metabolic derangements.

Aim of the Study

We aimed to determine the clinical types, frequencies and possible mechanisms of recurrent seizures in adults due to uremic syndrome of CKD and their independent predictors (clinical, laboratory and neuroimaging characteristics).

Patients and Methods

This was a cross-sectional observational study. It included 70 adults (male = 33; female = 37) with uremic syndrome due to CKD. They had age range of 18 to 60 years. Patients were recruited over a period of two years (January 2018- February 2020) from the departments of Internal Medicine and dialysis units of Assiut and Al-Azhar University Hospitals, Assiut, Egypt (tertiary referral centers). Patients were divided into those on dialysis or ESKD (stage 4-5: estimated glomerular filtration rate or eGFR: ≤ 15-30 ml/min) and those not on dialysis (stage 1-3: eGFR: < 60 but > 15 ml/min). The type of seizure was defined according to the International League Against Epilepsy (ILAE) [13]. Inclusion criteria were: (1) adult of 60 years old or less, (2) renal cause of uremia, (3) development of seizures after CKD onset. Exclusion criteria were: (1) pre- or post- renal causes of uremia, (2) CNS or other medical or surgical causes of seizures, (3) presence of positive family history of epilepsy, (4) history of head trauma, (5) history of drug abuse, and (6) history of prolonged use of known nephrotoxic agents.

The protocol of the study was approved by local ethical committees of Faculties of Medicine of Assiut (AUFM-188 /2018) and Al-Azhar Universities, Egypt. Informed consent was obtained from each participant. Participants underwent: (1) Medical and neurological histories and examinations. Interviewing of patients with uremic encephalopathy was done when they were not encephalopathic. (2) Laboratory investigations included: blood urea, creatinine, urinalysis, complete blood count (CBC), random blood sugar (RBS) level, arterial blood gases (ABG) (PaO_2, $PaCO_2$, HCO_3 and O_2 saturation), serum levels of total bilirubin, alanine (ALT) and aspartate (AST) aminotransferases, prothrombin time and concentration, INR, electrolytes (Ca^{2+}, Na^+, K^+, Mg^+ and phosphorus) and thyroid (T3, T4, TSH) and parathyroid hormones, (3) Electroencephalography (EEG), (4) Brain computed tomography (CT) or magnetic resonance imaging (MRI).

Statistical Analysis

SPSS version 22.0 for windows (Statistical Package for the Social Sciences Inc, Chicago III) was used for statistical analyses. Kolmogorov-Smirnov test was used to determine data distribution. Quantitative data were expressed as mean ± standard deviation (SD) as they were normally distributed. Comparative statistics were done using Student's t- test (two-tailed) for quantitative variables and Chi-square test for qualitative variables. Multiple regression analysis was done to determine the demographic, clinical, laboratory and neuroimaging variables which were independently associated with the occurrence of recurrent seizures. Data were expressed as 95% confidence intervals percentage (CI%). Statistical significance was considered with a probability < 0.05.

Results

Participants had mean age of 45.8 ± 3.4 years and duration of uremia of 5.5 ± 1.5 years. Forty-five (62.29%) had ESKD (stage 4 and 5) and on regular hemodialysis sessions (mean number of sessions = 3 ± 1; mean session duration = 3.5 ± 0.5 hours). Twenty-five (35.71%) had stage 3 kidney failure. They were on dietary control and supportive treatments. Nephritis (64.3%) and diabetic nephropathy (24.3%) were the most common causes of uremia due to CKD. Hypertension with or without ischemic heart disease were the comorbid medical diseases in 70%. The frequent laboratory abnormalities were hypocalcemia (70%), anemia (68.6%) and hypoalbuminemia (60.4%). Uremic encephalopathy was reported in 45.7% (Table 1). Myoclonic jerks were observed in the majority of patients (n = 48; 68.6%), in every patient with uremic encephalopathy (on dialysis) and in 40% (n =10) of patients not on dialysis. EEG of the majority of patients with myoclonus (67%) had spikes or poly-spikes and slow-wave

discharges which were in temporal relationship to the muscle action potentials (MAPs) associated with the myoclonic jerks. Epileptic EEG activity (spikes and spike-wave complexes) was reported in 24.3 % (n = 17) in absence of seizures (Figure 1). Eleven patients (15.7%; on dialysis = 6, not on dialysis = 5) developed recurrent seizures after the development of CKD. Six (54.55%) had GTC seizures, of them 4 (66.67%) had tetany, hypocalcemia (< 6 mg/dl), hyperparathyroidism and brain calcifications. Five (45.45%) had focal seizures to bilateral GTC, focal EEG epileptic brain activity and WHM's (Table 2). The most frequent MRI-brain abnormalities were WMH's (48.6%, n = 34). Focal encephalomalacia in cerebral hemispheres (lobar) and/or basal ganglia (iso-signal to CSF) were observed in 25.6%. There was no history of brain insults (cerebrovascular strokes) (Table 1, Figure 2). Bilateral brain calcifications were observed in 10% (n = 7) (Table 1, Figure 3). Compared to those without seizures, the majority of patients with seizures had ESKD (on hemodialysis), metabolic derangements (hyperphosphatemia and metabolic acidosis) and neuroimaging abnormalities (Table 1).

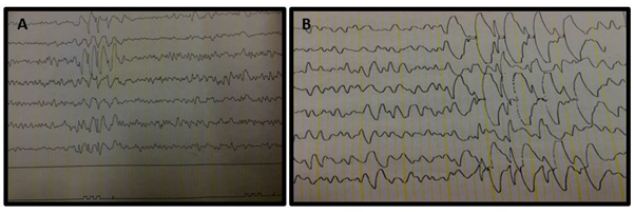

Figure 1: (A): EEG findings in a patient with uremic encephalopathy and had myoclonic jerks. It showed excess of delta and theta waves and multifocal spikes and spike-wave discharges. **(B):** EEG findings of a patient with uremic encephalopathy with no history of seizures. It showed background with excess theta and delta waves and generalized spike-wave complexes.

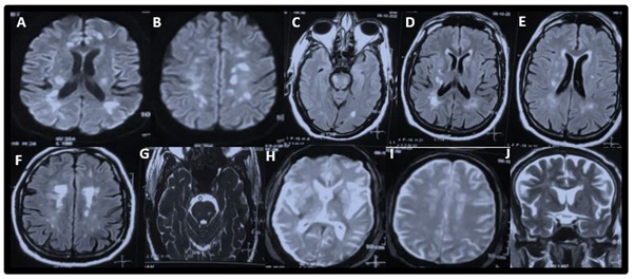

Figure 2: MRI-brain views (axial and coronal) of patient's (# 4) with recurrent focal motor to bilateral tonic-clonic. MRI-brain showed bilateral scattered hyperintense lesions in diffusion weighted images (DWI) (A and B), hyperintense lesions in fluid attenuated inversion recovery (FLAIR) (C-G) and hyperintense and hypointense lesions in T2-weighted images (T2WI) (i.e. WMH's) (H-J).

Multiple regression analysis showed that the presence of seizures was independently associated with the severity of kidney failure (i.e. higher urea and creatinine levels) (OR = 1.25, 95% Cl = 1.08-1.30, P = 0.01) and the presence of metabolic derangements (hypocalcemia and hyperphosphatemia) (OR = 2.44; 95% CI = 1.25-2.80, P = 0.01).

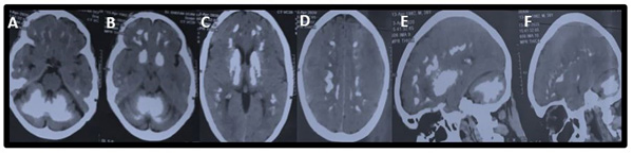

Figure 3: CT-brain views (axial and sagittal) of patient's (# 3) with recurrent GTC seizures. They showed bilateral calcifications in cerebellar and cerebral hemispheres and basal ganglia.

Discussion

There are few data in the literature regarding the types, prevalence and drug treatments of uremic seizures because "recurrent seizures" may also be a symptomatic manifestation of many causes and comorbidities of CKD. The progression of uremia due to CKD towards ESKD and its acute manifestations (as uremic encephalopathy with/or without metabolic derangements) are the most common precipitating factors of uremic seizures. In this study, we preferred to use the term uremic seizures instead of epilepsy according to ILAE (which is defined as ≥ 2 unprovoked seizures occurring > 24 h apart), because these seizures were often provoked by acute metabolic insults or due to the neurotoxic consequences of kidney failure. They were corrected when the underlying metabolic derangement has elapsed and without regular treatment with antiepileptic drugs (AEDs).

In this study, we observed increased frequency of focal or generalized seizures in temporal relation to the onset of uremic encephalopathy and its metabolic derangements. They disappeared after their correction [4], dietary control (e.g. avoiding diet containing high amounts of salts, potassium, protein and phosphate) and supplemental use of vitamin D [14]. We observed that 66.67% of patients with GTC seizures had tetany, hypocalcemia and hyperparathyroidism. Studies reported that in patients with uremia, seizures are common manifestations of uremic encephalopathy and its metabolic derangements (as hyperphosphatemia, hyponatremia and hypomagnesemia and acidosis) [15, 16]. It has also been observed that hyperphosphatemia frequently occurs with uremic syndrome due to failure to excrete phosphate by the damaged kidneys [17]. Excess phosphate forms complexes with calcium. This prevents the activation of vitamin D resulting in hypocalcaemia. In order to maintain normal blood calcium level, direct stimulation parathyroid hormone (PTH) occurs resulting in renal hyperparathyroidism [5]. PTH enhances the function of calcium transporters and increases the calcium content of the cerebral cortex [18]. Hyperparathyroidism also increases the permeability of neuronal membranes to sodium ions resulting in progressive depolarization and tetany [19]. Studies also found that tetany may occur with uremic syndrome despite the presence of acidosis which normally inhibits tetany due to hypocalcemia [5, 8].

In general, the incidence of uremic seizures due to CKD has been estimated to be ~ 10%. Uremic seizures have been categorized into: (1) acute symptomatic seizures in patients with epilepsy and developed CKD at some points of their lives: The break of seizures often occurs due to improper selection,

Table 1: Characteristics of the studied groups and in relation to presence or absence of recurrent seizures.

Demographic, clinical Laboratory and neuroimaging characteristics	**Patients** (n = 70)	**With seizures** (n = 11, 15.7%)	**Without seizures** (n = 59, 84.3%)	**P-value**
Demographic and clinical characteristics				
Male **Female**	33 (47.10%) 37 (52.90%)	4 (36.36%) 7 (63.64%)	29 (49.2%) 30 (50.8%)	0.228 0.230
Age; years Range Mean ± SD	 18-60 48.87 ± 8.36	 20-60 46.45 ± 14.85	 18-60 52.36 ± 6.28	 0.345
Duration of uremia; years Range Mean ± SD	 1-13 5.54 ± 1.53	 1-5 3.27 ± 1.27	 1-13 5.80 ± 1.62	 0.01
Comorbid medical conditions Hypertension and ischemic heart disease Hypothyroidism	 49 (70%) 2 (2.9%)	 3 (27.27%) 0	 46 (77.97%) 2 (3.39%)	 0.126 -
Cause of uremia Diabetes mellitus Glomerulonephritis Congenital kidney agenesis Systemic lupus erythematosus (SLE)	 17 (24.3%) 45 (64.3%) 4 (5.7%) 4 (5.7%)	 3 (27.27%) 6 (54.55%) 1 (9.09%) 1 (9.09%)	 14 (23.73%) 39 (66.10%) 3 (5.08%) 3 (5.08%)	 0.420 0.428 0.240 0.240
On dialysis **Not on dialysis**	45 (62.29%) 25 (35.71%)	6 (54.55%) 5 (45.45%)	39 (66.10%) 20 (33.90%)	0.255 0.238
Uremic encephalopathy	32 (71.11%)	4 (36.36%)	28 (47.46%)	0.256
Tetany	4 (5.7%)	4 (36.36%)	0	-
Type of seizures Generalized tonic-clonic seizures Focal seizures	 4 (5.71%) 7 (10%)	 4 (36.36%) 7 (63.64%)	 - -	 - -
Laboratory characteristics				
Hyponatremia	9 (12.86%)	1 (9.09%)	8 (13.56%)	0.320
Hyperkalemia	13 (18.57%)	0	13 (22.03%)	-
Hypomagnesaemia	8 (11.43%)	0	8 (13.56%)	-
Hypocalceemia	49 (70%)	11 (100%)	38 (64.41%)	0.001
Hyperphosphataemia	21 (30%)	7 (63.64%)	14 (23.73%)	0.001
Anemia	46 (68.57%)	6 (54.55%)	40 (67.8%)	0.358
Metabolic acidosis	24 (53.33%)	6 (54.55%)	18 (30.51%)	0.05
Neuroimaging characteristics				
Cerebral white matter ischemic lesions Cerebral brain infarctions Basal ganglionic ischemic lesions/infarctions Thalamic infarction Bilateral basal ganglionic calcification (Lentiform nuclei)	34 (48.57%) 12 (17.14%) 6 (8.57%) 1 (1.43%) 7 (10%)	6 (54.55%) 2 (18.18%) 3 (27.27%) - 4 (36.36%)	28 (47.46%) 10 (16.95%) 3 (5.08%) - 3 (5.08%)	0.352 0.646 0.05 - 0.01

Data were expressed as number (%); range and mean ± SD

P: significance for patients with seizures versus without seizures

loading, titration, and maintenance of AEDs. The latter could be due to altered drugs' pharmacokinetics with uremia. (2) acute symptomatic seizures without an established diagnosis of epilepsy due to complications of kidney failure (as brain edema due to uremic encephalopathy with/without metabolic derangements or hypertensive encephalopathy) [20, 21]. (3) acute symptomatic seizures during or just after dialysis due to hemodynamic instability [22]. (4) recurrent seizures in absence of encephalopathy or obvious metabolic derangements which could explain their occurrence. Studies [4, 9] found that uremic toxins (e.g. guanidino compounds) resulted in (a) inhibition of γ-amino-buyteric acid receptors (GABAARs), (b) activation of N-Methyl-D-Aspartate receptors (NMDARs), (c) lifting voltage dependent block from NMDARs, calcium influx through NMDARs ionophores and voltage gated calcium channels and activation of postsynaptic calcium triggered events. These result in excess nitric oxide, increase glutamate release and excitotoxicity. This is further supported by the

Table 2: The characteristics of patients with recurrent seizures.

#	Age and gender	Duration of uremia	Cause of uremia and comorbidities	Types and duration of seizures	Uremic encephalo-pathy	Laboratory findings	EEG findings	Imaging findings	Therapy
1	A 20-year-old female .	2 years	chronic glomerulonephritis	Focal motor to bilateral GTC seizures since 1.5 years and in temporal relation to encephalopathy	Present	- Hyponatremia (Na^{+} = 129 mmol/L) - Hypocalcemia (Ca^{+2} = 8.5 mg/dl). - Hypoalbuminemia (albumin = 3 g/L) - Anemia (RBCs count = 3 million/mcl; HGB = 8.5 mg/dl) - Metabolic acidosis (pH = 7.34; PO_2 = 90 mmHg; PCO_2 = 35 mmHg; HCO_3 = 16 MEq/L)	Focal (fronto-parietal) epileptic discharges	MRI: Normal	- Regular hemodialysis (3 week for 2-3 hours per session). - Correction of associated metabolic derangements
2	A 60-year old female	1 year	Diabetic nephropathy	Focal motor to bilateral GTC seizures since 1 year and in temporal relation to encephalopathy	Present	- Hypocalcemia (Ca^{+2} = 6.3 mg/dl) - Hypoalbuminemia (albumin = 3 g/L) - Anemia (RBCs count = 3 million/mcl; HGB = 7.7 mg/dl) - Metabolic acidosis (pH = 7.32; PO_2 = 85 mmHg; PCO_2 = 30 mmHg; HCO_3 = 12 MEq/L)	Focal (fronto-parietal) epileptic discharges	MRI: Left putamen infarction (old) and WMH's	- Regular hemodialysis (3 week for 3 hours per session).
3	A 30-year old female	5 years	- Chronic glomerulonephritis - Tetany	GTC seizures since 3 years.	Absent	- Hypocalcemia (Ca^{+2} = 5.5 mg/dl) - Hyperphosphatemia (7 mg/L); - Hyperparathyroidism (PTH = 96 pg/ml; normal = 10-65 pg/ml) - Metabolic acidosis (pH = 7.33; PO_2 = 87 mmHg; PCO_2 = 35 mmH; HCO_3 =15 MEq/L)	Generalized epileptic discharges	MRI: bilateral calcification in cerebral and cerebellar hemispheres and basal ganglia (Figure 3)	- Regular hemodialysis (3 week for 2-3.5 hours per session). - Use of phosphate binders (calcimimetics)
4	A 60-year old female	5 years	Chronic glomerulonephritis	- Focal motor to bilateral GTC seizures and multifocal myoclonic jerking. - They occurred since 4 years and in temporal relation to encephalopathy	Present	- Hypocalcemia (Ca^{+2} = 8 mg/dl) - Metabolic acidosis (pH = 7.30; PO_2 = 85 mmHg; PCO_2 = 34 mmHg; HCO_3 = 10 MEq/L)	Multifocal spike-wave complexes	MRI: WMH's (Figure 2)	- Regular hemodialysis (3 week for 2-3.5 hours per session) - Use of phosphate binders (calcimimetics)
5	A 49-year old male	3 years	- Chronic glomerulonephritis - Tetany	GTC seizures since 3 years	Absent	- Hypocalcemia (Ca^{+2} = 4.6 mg/dl) - Hyperphosphatemia (8 mg/L) - Anemia (RBCs count = 2.5 million/mcl; HGB = 7.8 mg/dl) - Hyperparathyroidism: (PTH = 115 pg/ml)	Generalized epileptic discharges	CT: Bilateral basal ganglionic calcification	- Supportive: vitamin D and iron supplements - Phosphate binders (calcimimetics)

6	A 32-year old male	3 years	- Congenital right kidney agenesis. - Hypertension	Focal motor to bilateral GTC seizures since 3 years	Present	- Hypocalcemia (Ca^{+2} = 6.5 mg/dl), - Hypoalbuminemia (albumin = 3.1 g/L) Anemia (RBCs count = 3.4 million/mcl; HGB = 7.7 mg/dl) - Metabolic acidosis (pH = 7.35; PO_2 = 89 mmHg; PCO_2 = 39 mmHg; HCO_3 = 16 MEq/L)	Focal (fronto-parietal) epileptic discharges	MRI: WMH's	- Regular hemodialysis (3 week for 2-3 hours per session). - Irregular treatment with CBZ
7	A 55-year old male .	4 years	Chronic glomerulonephritis	Focal motor to bilateral GTC seizures since 4 years and in temporal relation to encephalopathy	Present	- Hypocalcemia (Ca^{+2} = 7.3 mg/dl) - Hyperphosphatemia (5.6 mg/L) Hypoalbuminemia (albumin = 3.1 g/L) - Anemia (RBCs count = 2.5 million/mcl; HGB = 7.8 mg/dl) - Metabolic acidosis (pH = 7.33; PO_2 = 92 mmHg; PCO_2 = 30 mmHg; HCO_3 = 13 MEq/L)	Focal (fronto-parietal) epileptic discharges	MRI: Left globus pallidus infarction (old) and WHM's	- Supportive: vitamin D and iron supplements
8	A 52-year old female	4 years	Diabetic nephropathy	Focal motor-sensory to bilateral tonic clonic seizures since 2 years	Absent	- Hypocalcemia (Ca^{+2} = 6 mg/dl) - Hyperphosphatemia (7 mg/L)	Focal (parieto-occipito-temporal) epileptic discharges	MRI: bilateral basal ganglia and right occipital infarctions and WMH's	- Phosphate binders (calcimimetics) - Regular treatment with CBZ
9	A 60-year old male	2 years	- Hypertension - Ischemic heart disease - Tetany	GTC seizures since 1 year	Absent	- Hypocalcemia (Ca^{+2} = 5.6 mg/dl) - Hyperphosphatemia (7 mg/L) - Anemia (RBCs count = 1.8 million/mcl; HGB = 5.6 mg/dl) - Hyperparathyroidism: (PTH = 9 pg/ml)	Normal	MRI: bilateral basal ganglia calcifications	- Supportive: vitamin D and iron supplements - Phosphate binders (calcimimetics)
10	A 33-year old female	3 years	Systemic lupus erythematosus	Focal motor-sensory to bilateral tonic clonic seizures	Absent	- Hypocalcemia (Ca^{+2} = 7.8 mg/dl) - Hyperphosphatemia (5.7 mg/L) - Anemia (RBCs count = 3.2 million/mcl; HGB = 9 mg/dl)	Focal (fronto-parietal) epileptic discharges.	MRI: WHM's Lacunar infarctions in the parietal lobe.	Oral supplements with calcium and vitamin D
11	A 60-year old female	4 years	- Chronic glomerulonephritis - Hypertension - Ischemic heart disease - Tetany	GTC seizures since 2 years	Absent	- Hypocalcemia (Ca^{+2} = 5.2 mg/dl) - Hyperphosphatemia (5.3 mg/L) Hypoalbuminemia (albumin = 3 g/L) - Hyperparathyroidism: (PTH = 120 pg/ml)	Generalized epileptic discharges	CT: Bilateral basal ganglionic calcification	- Oral supplements with calcium and vitamin D - Pphosphate binders (calcimimetics)

finding that methyl guanidine (a uremic toxin) can induce uremic twitch-convulsive syndrome, a condition similar to uremic encephalopathy with seizures [22].

In this study, no one developed seizures due to dialysis. Previous studies reported seizures during or shortly after the hemodialysis and this has been attributed to the hemodynamic and biochemical changes associated with the dialysis process [21].

We also found epileptic EEG activity (spikes and spike-wave complexes) in 24.3% in absence of history of seizures. Studies observed epileptic discharges (spikes and spike-slow wave complexes) in 14% of patients in absence of seizures. [23] Hughes et al. [23] observed that the presence of EEG epileptiform abnormalities in absence of seizures could increase the risk for occurrence of future seizures and its recurrence than the absence of epileptiform abnormalities in EEG.

In this study, the majority of patients did not use AEDs and were not compliant on the prescribed AEDs. The main therapies of recurrent seizures with uremia were (1) increasing the frequency of hemodialysis for at least 3 times per week and duration of dialysis to be 3.5 hours per session, (2) correction of metabolic derangements, (3) dietary control, (4) vitamin D supplements, (5) phosphate binders (calcimimetics) were used for treatment of hyperparathyroidism to reduce phosphate levels [24]. The lack of use of AEDs could be attributed to the following: (1) the infrequent seizure occurrence in those who were not on dialysis, (2) seizures' occurrence in temporal relationship to the dialysis time and improved after dialysis, (3) fear of deterioration of kidney function or occurence of AED's drug toxicity.

In this study, we observed that the prescribed AED was carbamazepine (CBZ) which is considered a correct choice in the setting of uremic syndrome because of the following: (1) CBZ is mainly eliminated by the liver, and (2) it is highly protein bound with only a small proportion of the total drug persists in the free active state [20]. In general, the most recommended AEDs in renal impairment and haemodialysis are those that are mainly eliminated by the liver (as benzodiazepine, CBZ, phenytoin and valproate [25, 26]). However, supplemental drug doses may be required due to excess elimination by dialysis [27]. On the other hand, drug monitoring of free drug level is required because the majority of patients of CKD also frequently have hypoalbuminemia which also increases the possibility of drugs' toxicity [25].

Limitations of the Study

(1) Small sample size may result in statistical bias. However, we preferred to evaluate homogenous groups of patients with exclusion of history of epilepsy prior to CKD's onset.

(2) Despite obvious causes of recurrent seizures in some patients, however, we cannot exclude the possible contribution of the original cause of CKD and the comorbid medical conditions as causes of seizures (e.g. brain vascular angiopathy due to diabetes or hypertension). This is supported by the findings of high frequency of WMH's which are common in diabetes, hypertension and anemia.

(3) Although myoclonus is one type of seizures, however, among specialized physicians, myoclonic jerking is considered as abnormal involuntary movements and has different pathophysiologic mechanisms.

Conclusion

Recurrent seizures (generalized and focal) are common with progression of kidney failure. There are heterogeneous causes of uremic seizures, types, frequencies, courses and consequences. The obvious causes in this study were metabolic derangements (hypocalcemia, hyperphosphatemia and brain calcification caused by renal hyperparathyroidism). Improvements of seizures usually occur with improvement of kidney function (e.g. hemodialysis, dietary control, etc.) and correction of metabolic derangements. However, AEDs (e.g. CBZ) may be effective for treating uremic seizures which could not be explained by the presence of obvious encephalopathy or metabolic derangements.

Authors' Contribution

SAH, AFE and SKA did the clinical evaluation of the patients, blood sampling, participated in the design of the study, statistical analyses and drafting of the manuscript. All authors read and approved the final manuscript.

Conflict of Interests

None declared

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