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General Medicine

TO STUDY THE PREVALENCE OF NEUROLOGICAL MANIFESTATIONS IN CKD PATIENTS IN BUNDELKHAND REGION

Dr. N.S. Sengar	Professor, Department of Nephrology, M.L.B. Medical College, Jhansi.
Dr. Arvind Kankane	Associate Professor, Department of Medicine, M.L.B. Medical College, Jhansi.
Dr. Mohd. Imran*	Junior Resident, Department of Medicine, M.L.B. Medical College, Jhansi. *Corresponding Author
Dr. Gopambuj Singh Rathod	Junior Resident, Department of Medicine, M.L.B. Medical College, Jhansi.
Dr. Bhawna Rai	Junior Resident, Department of Medicine, M.L.B. Medical College, Jhansi.

ABSTRACT

Introduction: Chronic kidney disease (CKD) is a rapidly growing global health problem, with a prevalence of 15% in developed nations. CKD can occur as the result of a primary renal disorder or as a complication of multisystem disease. Diabetes is now the most common cause of CKD in developed countries, whereas in the developing world, inflammatory diseases of the kidney, particularly glomerulonephritis and interstitial nephritis, remain the most common causes. The most common neurological manifestation were cerebrovascular accident (stroke), myopathy, peripheral neuropathy, GTCS, Dementia, Disequilibrium syndrome, Orthostatic hypotension and Restless Leg Syndrome.

Aim: To study the prevalence of neurological manifestations in Chronic Renal Failure patients in Bundelkhand Region of Uttar Pradesh.

Materials and Methods: This study was a cross sectional study conducted in M.L.B Medical College, Jhansi (U.P.). This study included CKD patients coming to Department of General Medicine, M.L.B. Medical College, Jhansi during the period March 2018 to October 2019, study comprises of 170 patients. Out of these, 95 patients were having neurological manifestation.

Results: Study observed that, neurological manifestation was more common among male (67.37%) of age group 51 to 60 yrs (28.24%) and most of them were found smoker (56.84%) and hypertension (84.21%). Most of the patients having neurological manifestation were on maintenance haemodialysis (61.05%). We divided all the number of cases in six age group, majority of cases were found in 51-60 yrs age group i.e. 48 (28.24%) followed by 41-50 yrs age group i.e. 29 (17.06%) and 18 (10.59%) patients were found in 30 yrs, 31-40 yrs, and >70 yrs of age group respectively. The most common neurological manifestation were cerebrovascular accident (stroke) (33.68%), myopathy (17.89%), peripheral neuropathy (14.74%), GTCS (8.42%), Dementia (8.42%), Disequilibrium syndrome (7.37%), Orthostatic hypotension (6.32%) and Restless Leg Syndrome (3.1%)

Conclusion: Neurological manifestations are highly prevalent in CKD and are a major cause of morbidity and mortality. Both CNS and PNS complications were most apparent at end-stage disease i.e. CKD stage V. neurological manifestation occurred in our study were mainly associated with hypertension, anemia, albuminuria, electrolytes abnormalities (like hyperphosphatemia, hyponatremia), raised blood urea nitrogen level. So early detection and management of these factors in CKD patients represents a window of opportunity to reduce their impact in later stages of CKD.

KEYWORDS : Chronic kidney disease, neurological complications, uraemic neuropathy, uraemic encephalopathy, cognitive dysfunction, peripheral neuropathy, autonomic neuropathy

INTRODUCTION

Chronic Kidney Disease (CKD) is defined according to the presence or absence of kidney damage and level of kidney function—irrespective of the type of kidney disease.

Accordingly Defined As[1] :

1.Kidney damage for >3 months as defined by structural or functional abnormalities of kidneys with or without decreased GFR, manifest by either.

a. Pathological abnormalities,

b. Abnormalities in markers of kidney damage including persistently increased protein excretion, urine sediment examination or dipstick for red blood cells and white blood cells or imaging studies of the kidneys.

2.eGFR < 60ml/min/1.73m2 for >3 months with or without kidney damage.

The two main causes of CKD are diabetes and high blood pressure, which are responsible for up to two-thirds of the cases. Glomerulonephritis, polycystic kidney disease, lupus and obstructive lesions are other causes of CKD[2].

CKD encompasses a spectrum of disease, ranging from mild kidney damage, which can be asymptomatic and is only detected by blood and urine testing, through to end-stage disease, in which kidney function is impaired to such an extent that the retention of metabolic waste products, salt and water becomes potentially fatal.

A strict collaboration between nephrologists, neurologists and other specialists may decrease the social burden of these neurological complications of CKD by reducing morbidity and mortality of chronic kidney disease patients.

Therefore, the present study was undertaken to studied patients of chronic kidney disease and assessed the prevalence of neurological manifestation in CKD patients like cerebrovascular accident (stroke), myopathy, peripheral neuropathy, GTCS, Dementia, Disequilibrium Syndrome, Orthostatic Hypotension and Restless Leg Syndrome.

AIMS AND OBJECTIVES

- To study the prevalence of neurological manifestations in Chronic Renal Failure patients in Bundelkhand Region of Uttar Pradesh.
- To study the clinical and diagnostic characteristics of CKD patients treated through different strategies of management.
- Evaluate the involvement of Autonomic Nervous System (ANS), Peripheral Nervous System (PNS) and Central Nervous System (CNS) in CKD patient.

MATERIAL AND METHODS:

This study was a cross sectional study conducted in M.L.B Medical College, Jhansi (U.P.). This study included CKD patients coming to Department of General Medicine, MLB Medical College, Jhansi during the period March 2018 to October 2019, minimum 170 patients were taken for the study. The study was performed after obtaining permission from the Institutional ethics committee and the

identity of the patients was not revealed. The study was done to evaluate the prevalence of neurological manifestations in CKD patients.

Calculation of eGFR by Cockroft-Gault Equation which is given by:

$$\frac{(140\text{-age}) \times \text{Body Wt. (kg)}}{72 \times \text{Pcr. (mg/dl)}}$$

Multiplied by 0.85 for women.

Stages of CKD defined by GFR.ml/min/1.73 m2
·Stage 0: >90 ml/min/1.73 m2 with risk factors for CKD
·Stage 1: ≥90 ml/min/1.73 m2 with demonstrated kidney damage
·Stage 2: 60-89 ml/min/1.73 m2
·Stage 3: 30-59 ml/min/1.73 m2
·Stage 4: 15-29 ml/min/1.73 m2
·Stage 5:< 15ml/min/1.73 m^2.

Inclusion Criteria
- All patients who are diagnosed as Chronic Kidney Disease

Exclusion Criteria
- CKD patient age < 15 years
- Any patients having pre-existing renal disease.
- Patients on peritoneal dialysis
- Patients had received renal transplant.
- Patients having AKI with neurological manifestation
- CKD patient having multisystem involvement.

Methodology
All the patients meeting inclusion and exclusion criteria was evaluated thoroughly. History collection, clinical examination, ABG, USG abdomen, laboratory investigations such as complete blood count, lipid profile, blood sugar level, urine analysis, and other routine investigations like serum parathyroid hormone level were performed as a part of routine diagnosis and treatment for all the patients.

RESULTS
This study was a hospital based cross sectional study comprises of 170 patients. Out of these, 95 patients were having neurological manifestation it was observed that neurological manifestation were more common among male (67.37%) of age group 51 to 60 yrs (28.24%) and most of them were found smoker (56.84%) and hypertension (84.21%). Most of the patients having neurological manifestation were on maintenance haemodialysis (61.05%).

Table 1: Age Wise Distribution Of Cases.

AGE GROUP (in years)	No. of Cases (n=170)	Percentage
30	18	10.59%
31-40	18	10.59%
41-50	29	17.06%
51-60	48	28.24%
61-70	39	22.94%
>70	18	10.59%
Total	**170**	**100%**

We divided all the number of cases in six age group, majority of cases were found in 51-60 yrs age group i.e. 48 (28.24%) followed by 41-50 yrs age group i.e. 29 (17.06%) and 18 (10.59%) patients were found in 30 yrs, 31-40 yrs, and > 70 yrs of age group respectively.

The most common neurological manifestation were cerebrovascular accident (stroke) (33.68%), myopathy (17.89%), peripheral neuropathy (14.74%), GTCS 8.42%, Dementia (8.42%), Disequilibrium syndrome (7.37%), Orthostatic hypotension (6.32%) and Restless Leg Syndrome (3.1%).

Table 2: Distribution of various neurological manifestation in CKD patients.

Neurological Manifestation		No. of Cases (n'=95)	%
Cerebrovascular accident (Stroke) (N=32/33.68%)	Infarct	23	24.21%
	Haemorrhage	09	9.47%
MYOPATHY		17	17.89%
Peripheral neuropathy		14	14.74%
GTCS		08	8.42%
Dementia		08	8.42%
Disequilibrium syndrome		07	7.37%
Orthostatic hypotension		06	6.32%
Restless leg syndrome		03	3.16%
Total		95	100%

This study also showed that 74.74% patients were in CKD stage V followed by 16.84% in stage IV.

Table 3: Prevalence of neurological manifestation in various stages of CKD patients.

CKD Stage	No. of Cases (n=170)	No. case having neurological manifestation (n'=95)	No. case not having neurological manifestation (n'= 75)
I	0	0	0
II	1	1 (1.05%)	0 (0%)
III	10	7 (7.37%)	3 (4.00%)
IV	27	16 (16.84%)	11 (14.67%)
V	132	71 (74.74)	61 (81.33%)
Total	170	95 (100%)	75 (100%)

Table 4: Factors Affecting Various Neurological Manifestations

Neurological manifestation (n=95)		DM		HTN		Anemia		S.creat. (mg/dl)		Pt. on RRT		Proteinuria		S.Albumin (mg/dl)		BUN (mg/dl)	
		Yes	No	Yes	No	Yes	No	>8	≤8	Yes	No	Yes	No	<3.5	>5.5	Normal ≤20	Abnorm 1>20
Cerebrovascular accident (Stroke)	INFARCT (23)	5	18	21	2	17	6	13	10	7	16	16	7	9	14	0	14
	HEMORRAHGE (9)	3	6	6	3	6	3	6	3	5	4	7	2	3	6	0	9
MYOPATHY (17)		14	3	16	1	13	4	12	5	13	4	13	4	9	8	0	17
Peripheral neuropathy (14)		2	12	12	2	10	4	8	6	8	6	11	3	7	7	0	14
GTCS (8)		0	8	7	1	5	3	5	3	7	1	6	2	3	5	0	8
Dementia (8)		3	5	7	1	6	2	6	2	6	2	6	2	5	3	0	8
Disequilibrium syndrome (7)		1	6	5	2	7	0	5	2	7	0	4	3	4	3	0	7
Orthostatic hypotension (6)		0	6	4	2	3	3	5	1	3	3	5	1	2	4	0	6
Restless leg syndrome (3)		1	2	2	1	2	1	0	3	2	1	3	0	2	1	0	3

Table 5: Factors Affecting Various Neurological Manifestations

Neurological manifestation (n=95)		Ca++ (mg/dl)		Na+ (meq/l)		S.K+ (meq/l)		$S.PO_4^-$ (mg/dl)		PTH (pg/ml)		MMSE	
		Normal (9-11)	Abnormal (<9 &>11)	Normal (135-145)	Abnormal (<135 &>145)	3.5-5	<3.5 &>5	2.5-4.5	>4.5	☐ 70	< 70	Normal (☐23)	Abnormal (<23)
Cerebrovascular accident (Stroke)	INFARCT (23)	1	22	15	8	18	5	2	21	22	1	0	0
	HEMORRAHGE (9)	4	5	3	6	4	5	2	7	5	4	0	0
Myopathy (17)		2	15	13	4	11	6	3	14	17	0	17	0
Peripheral neuropathy (14)		1	13	12	2	7	7	2	12	13	1	14	0
GTCS (8)		1	7	3	5	3	5	0	8	7	1	0	0
Dementia (8)		6	2	6	2	4	4	2	6	2	6	0	8
Disequilibrium syndrome (7)		2	5	0	7	3	4	0	7	5	2	0	0
Orthostatic hypotension (6)		1	5	4	2	4	2	1	5	5	1	6	0
Restless leg syndrome (3)		1	2	1	2	2	1	2	1	2	1	3	0

DISCUSSION
Out of 170 patients, majority of patients were male i.e. 116 (68.24%) and rest were female i.e. 54 (31.76%). Out of these, 95 patients having neurological manifestation, 64 (67.37%) were male and rest 31 (31.63%) patients were female. Age of the patients varied from minimum of 15 yrs and maximum of 86 yrs, meanSD was 53.8515.09 and majority of patients included in the study were in 51-60 yrs of age group. Which is support by a study conducted by **S.G. Shyam et al (2016)[3] and P.Rama et al (2010)[4]**

Outof 170 cases, 95 cases were having neurological manifestations, the prevalence of neurological manifestations in our study was 55.88%, out of these patients,32 (33.68%)were having Cerebrovascular accident (Stroke) followed by Mayopathy 17 (17.89%), peripheral neuropathy 14 (14.74%) and rest of cases having GTCS, Dementia, Disequilibrium Syndrome, Orthostatic Hypotension and Restless Leg Syndrome i.e. 8 (8.42%), 8 (8.42%), 7 (7.37%), 6 (6.32%), and 3 (3.16%) respectively were found.

In our study, most of the patients were hypertensive (84.37%) andanemic (71.87%). The most common neurological complication was cerebrovascular accident (stroke) 33.68%, out of these 24.21% were having cerebral infraction and 9.47% were having cerebral hemorrhage.

A study done by **Tanja Hojs Fabjan et al (2014)[5]** also concluded that ischemic stroke was more common than hemorrhagic stroke in

CKD patients.

A study done by **Thorgeirsson G et al (1978)[6] and Bundgaard M et al (1984)[7]**showed that the hypertension was a major risk factor for both ischemic and hemorrhagic stroke.

Similarly in our study, most of the cerebrovascular accident (stroke) were in later stages of CKD i.e. stage III, IV and V.

Myopathy:
The prevalence of myopathy in our study was 17.89% A significant correlation also exists between glomerular filtration rate (GFR) and exercise tolerance or muscle peak oxygen uptake (peak VO2) Uremic myopathy usually appears with a GFR under 25 mL/min and is rare with a higher GFR **Clyne, N et al (1996)[8]**. In our study,out of 17 patients, 14 (82.35%) patients were present in CKD stage V.

The specific type of renal replacement therapy (haemodialysis) also appears to play a role. It has generally been shown that exercise tolerance in predialysis patients is greater than that in hemodialysis patients and there are no significant differences between patients undergoing peritoneal dialysis or hemodialysis **Painter P et al (1986)[9]**. In our study, 15 (88.23%) patients were on RRT (Haemodialysis) and having myopathy

Although a close relationship exists between anemia and exercise limitation in uremic patients **Metra M. et al (1991)[10]**. In our study, majority of myopathy patient were anemic i.e. 13 (76.47%) out of 17 patients.

Certain systemic diseases, particularly arterial hypertension, have been associated with uremic myopathy **Casaburi R. et al (1997)[11]**. In our study, majority of myopathy patients were hypertensive i.e. 16 (94.11%) out of 17 patients.

Diabetic patients undergoing dialysis have a higher prevalence and more severe forms of uremic myopathy **Thage O et al (1970)[12]**. In our study,14(82.35%) out of 17 patients were diabetic.

Secondary hyperparathyroidism has been clearly associated with uremic myopathy **Massry S.G et al (1984)[13]**. Parathyroid hormone increases the entry of calcium into myocytes in a dose-dependent manner by enhancing calcium influx through the activation of the G protein voltage-dependent calcium channel. In our study, all the 17 (100%) patients were having hyperparathyroidism.

Peripheral Neuropathy:
In our study, prevalence of peripheral neuropathy 14.74% A study conducted by **M. Madhusudhana Babu et al., (2015)[14]** concluded that the peripheral nerves dysfunction was more prevalent in elder age (>65 years) subjects.

Most common type of neuropathy present in our study was distal, symmetric, mixed sensory motorpolyneuropathy. Out of 14 patients having peripheral neuropathy 11 (78.57%) of patients were males, 12 (85.71%) were hypertensive and 10 (71.43%) were >65 yrs of age.

Dementia:
Out of total 170 patients, 95 were having neurological manifestation, out of these,dementia was present in 8 (8.42%) patients. In these patients,factors affecting dementia were HTN **7 (87.5**%), H/O hemodialysis**6 (75**%), Proteinuria **6 (75**%).

The prevalence of dementia in our study was 8.42%, several other studies showed the prevalence of dementia in CKD patient varies from 30%-60% **Kurella M et al (2004)[15] and Antoine V et al (2004)[16].**

In our study, majority of patients having dementia were having mean age 67.62 yrs. and mean MMSE score among the whole sample (170 patient) was 18.512.8 but among the patients having dementia (8 patients), the MMSE score was 16.5.This showed that the dementia patients were having less MMSE score in comparison to all 170 patients.

Cognitive impairment in CKD patients is not limited to patients with stage 5 CKD. Several cross-sectional studies have suggested its occurrence in earlier stages of kidney disease. Thus, estimated GFR (eGFR) was inversely related to global performance in global cognitive function tests (**Kurella M et al., (2004)[15] Hailpern SM et al (2005)[17] and O.G. Egbiet al., (2015)[18]**. In our study 6 (75%) out of 8 patients were in stage V and rest 1 patient in stage III, IV each.

Dialysis Dysequilibrium Syndrome (DDS):
Dialysis disequilibrium is most likely to occur in pediatric or older adult patients, patients with severe azotemia, and patients undergoing high-efficiency hemodialysis; however, it has also been reported in patients undergoing peritoneal dialysis and maintenance hemodialysis **Fukushige M et al (1971)[19]**. In our study, all 7 (100%) patients were on renal replacement therapy (haemodialysis), out of 7 patients having DDS, 5 (71.43%) patients were of older age group while 2 (28.57%) patients were of pediatricage group.

Other etiologies include hypo-and hypertension, metabolic disturbances like hypoglycemia, hyperand hyponatremia, hyper-phosphatemia, uremia, medication associated and stress **Gottschalk CW et al (1997)[20]**. In our study out of 7 patients having DDS, all the 7 (100%) patients had hyperphosphatemia and 5 (71.43%) patients had hyponatremia.

Generalized Tonic Clonic Seizure (GTCS):
In our study, the observed occurrence of seizures was8.42%. In this way, our data is in agreement with previous studies, with an estimated incidence of seizure of approximately 10% in patients with chronic renal failure **Bergen DC et al (1994)[21]**.

Rapid increases in blood urea nitrogen (BUN) may be a potent stimulus for seizures, but the presence of so many co-variant metabolic abnormalities makes it difficult to assign causation to any single factor. The serum BUN to calcium ratio has been offered as a good predictor of convulsions **Kirschbaum BB et al (1989)[22]**. In our study all the patients i.e. 8 (100%) had high serum blood urea nitrogen level (BUN) and our study concluded that the prevalence of GTCS was more in later stages of CKD i.e. stage V which is 100%.

Hypertension, particularly severe and uncontrolled; increase the risk of unprovoked seizures in older individuals **Dalby NO et al (2001)[23]; Salerno JA et al (1992)[24] and Hauser WA et al (1990)[25]**. In our study 7 (87.5%) out of 8 patient were hypertensive.

Renal failure may be accompanied by a reduction in glomerular and/or tubular functions, a rise in total body water with increased extracellular water, variable degrees of hypoalbuminemia, electrolyte imbalance, uremia, and functional change **Bergen et al (1994)[1] and Reindenberg MM et al., (1978)[26]**. In our study, all the patients (100%) had electrolyte abnormalities andhigh serum blood urea nitrogen level (BUN). Out of 8 patients, 3 (37.5%) had Hpoalbuminemia.

Orthostatic Hypotension:
Orthostatic hypotension (OH), a manifestation of autonomic dysfunction, is associated with incident hypertension **Rose KM et al (2002)[27] Perneger TV et al (1993)[28] and Iseki K et al., (1996)[29]**. In our study, out of 6 patients 4 (66.67%) were hypertensive, majority of patients were middle age group (mean age 40.83 yrs).

OH was associated with 76% increased risk of albuminuria, OH was independently associated with an increased risk of incident CKD and presence of increased albuminuria at follow up. **N Franceschini et al (2010)[30]**. In our study 5 (83.33%) out of 6 patients had albuminuria.

Restlessleg Syndrome :
RLS occurs in 3–15% of the general population and in 10–30% of patients on maintenance dialysis. RLS may lead to severe sleep onset or maintenance insomnia, and greatly impaired quality of life **Miklos Z. Molnar et al (2012)[31]**. In our study prevalence of restless leg syndrome was3.15%.66.67% patients

were on Renal Replacement therapy (Haemodialysis).

Studies report rates of diagnosis of the disease in this population ranging from 17 to 62% **Andreia Freire de Menezeset al (2018)**[32]. The pathophysiology of RLS is still obscure, and its genesis may be uremia, as well as iron deficiency **S. Clemens et al (2006)**[33]. In our study, 3 (100%) patients were having high blood urea nitrogen level (BUN).

Additionally, in dialysis patients it has been suggested that anemia, regardless of iron stores, may be the major cause of RLS development **La Manna G et al (2011)**[34]. In our study 2 (66.67%) patients were found anemic.

CONCLUSIONS

Neurological manifestationsare highly prevalent in CKD and are a major cause of morbidity and mortality. Presentations of altered mental status (Acute encephalopathies)may be differentiated according to acute vs. chronic CNS derangements. Chronic conditions such as stroke, myopathy, peripheral neuropathy and dementia require long-term risk management strategies to optimise outcomes in CKD patients. Acute encephalopathies may be caused by a wide variety of metabolic derangement, common in CKD patients and require rapid treatment. Physical disability in chronic CNS derangements was caused by cerebrovascular accident (stroke), myopathy, peripheral neuropathy andorthostatic hypertension. Both CNS and PNS complications were most apparent at end-stage disease i.e. CKD stage V. neurological manifestation occurred in our study were mainly associated with hypertension, anemia, albuminuria, electrolytes abnormalities (like hyperphosphatemia, hyponatremia), raised blood urea nitrogen level. So early detection and management of these factors in CKD patients represents a window of opportunity to reduce their impact in later stages of CKD.

As our center was a major tertiary care center in Bundelkhand region it cateredtoa large population.Our study was a cross-sectional study, with small sample size and conducted at a single centre. With the help of our study, we can focus on the major causes that predispose CKD patients to developing neurological manifestations like stroke, myopathy, peripheral neuropathy, dementia etc. Further larger studies involving multiple centres are required focusing on the occurrence of various neurological manifestations in CKD patients and timely interventionsthat can prevent the occurrence of neurological manifestation in CKD patients.

REFERENCES:

1. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, et al. Kidney disease: Improving Global Outcomes (KDIGO) CKD work group: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):5–14.
2. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, et al. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):19–62.
3. S.G. Shyam Lakshman,1 P. Ravikumar,corresponding author2 Giridhari Kar,3 Dwijen Das,4 Kallol Bhattacharjee,5 and Prithwiraj Bhattacharjee6.A Comparative Study of Neurological Complications in Chronic Kidney Disease with Special Reference to its Stages and Haemodialysis Status.Published online 2016 Dec 1. doi: 10.7860/JCDR/2016/22815.8947.
4. Rama P, Matuska S, Paganoni G, Spinelli A, De Luca M, Pellegrini G. Limbal stem-cell therapy and long-term corneal regeneration. N Engl J Med. 2010 Jul 8;363(2):147-55. doi: 10.1056/NEJMoa0905955. Epub 2010 Jun 23. PubMed PMID: 20573916.
5. Tanja Hojs Fabjan et al., Radovan Hojs. Stroke and renal dysfunction. European Journal of Internal Medicine 25 (2014) 18–24
6. G. Thorgeirsson and A. L. Robertson, Jr.The vascular endothelium-pathobiologic significance.Am J Pathol. 1978 Dec; 93(3): 803–848.
7. Bundgaard M: The three-dimensional organization of tight junctions in a capillary endothelium revealed by serial-section electron microscopy. J Ultrastruct Res 88:1–17, 1984
8. Clyne, N. Physical working capacity in uremic patients. Scand J Urol Nephrol. 1996; 30: 247–252
9. Painter, P., Rehak-Messer, D., Hanson, P. et al. Exercise capacity in hemodialysis, CAPD, and renal transplant recipients. Nephron. 1986; 42: 47–51
10. Metra, M., Cannella, G., La Canna, G. et al. Improvement in exercise capacity after correction of anemia in patients with end-stage renal failure. Am J Cardiol. 1991; 68: 1060–1066
11. Casaburi, R. Rehabilitation exercise training in chronic renal failure. in: J.D. Kopple, S.G. Massry (Eds.)Nutritional Management of Renal Diseases. Williams & Wilkins, Baltimore; 1997: 817–842
12. Thage, O. Metabolic neuropathies and myopathies in adults. Clinical aspects. Acta Neurol Scand.1970; 46: 120–126
13. Massry, S.G. Parathyroid hormone and uremic myocardiopathy. Contrib Nephrol. 1984; 41: 231–239.
14. Madhusudhana Babu M et al. Clinical manifestation and prevalence of peripheral neuropathy and nerve dysfunction in patients with chronic kidney disease. Int. J. Res. Med. Sci. 2015 : 3(2):451-455
15. Kurella M, Chertow GM, Luan J, Yaffe K: Cognitive impairment in chronic kidney disease. J Am Geriatr Soc 52: 1863–1869, 2004
16. Antoine V, Souid M, André C, Barthélémy F, Saint-Jean O. Symptoms and quality of life of hemodialysis patients aged 75 and over. Nephrologie 25: 89–6, 2004
17. Hailpern SM, Melamed ML, Cohen HW, Hostetter TH: Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: Third National Health and Nutrition Examination Survey (NHANES III). J Am Soc Nephrol 18: 2205–2213, 2007
18. Oghenekaro Godwin Egbi1, Olubunmi Ogunrin2, Efosa Oviasu2.Prevalence and determinants of cognitive impairment in patients with chronic kidney disease: A cross-sectional study in Benin City, Nigeria.Year : 2015 | Volume : 14 | Issue : 2 | Page : 75-81
19. Fukushige M, Tado O, Matsuki S, et al: Hemodialysis with Kiil-type artificial kidney—clinical study on disequilibrium syndrome. Hinyokika Kiyo 17(2):89–99, 1971.
20. Gottschalk CW, Fellner SK. History of the science of dialysis. Am J Nephrol. 1997;17(3–4):289–298.
21. Bergen DC, Ristanovic R, S. Seizures and renal failures. Int J Artif Organs 1994;17:247-251
22. B.B. Kirschbaum, A.C. Schoolwerth.Hyperaluminaemia Associated with Oral Citrate and Aluminium Hydroxide.First Published January 1, 1989 Research Article https://doi.org/10.1177/096032718900800108
23. Dalby NO, Mody I. The process of epileptogenesis: a pathophysio-logical approach. Curr Opin Neurol 2001;14:187-192.
24. Salerno JA, Murphy D G, Horwitz B, De Carli C, Haxby JV, Rapoport SL, Shapiro MB. Brain atrophy in hypertension: a volumetric magnetic resonance imaging study. Hypertension 1992;20:340-348
25. Hauser WA, Hesdorffer DC. Epilepsy: frequency, causes and consequences. New York: Demos, 1990.
26. Reidenberg MM, Levy M, Warner H, Coutinho CB, Schwartz MA, Yu G, Cheripko J. Relationship between diazepam dose, plasma level, age, and central nervous system depression. Clin Pharmacol Ther. 1978 Apr;23(4):371-4. PubMed PMID: 630787.
27. K M Rose, I Holme, K C Light, A R Sharrett, H A Tyroler & G Heiss.Association between the blood pressure response to a change in posture and the 6-year incidence of hypertension: prospective findings from the ARIC study.Journal of Human Hypertension volume 16, pages771–777(2002)
28. Perneger TV, Nieto FJ, Whelton PK, Klag MJ, Comstock GW, Szklo M. A prospective study of blood pressure and serum creatinine. Results from the 'Clue' Study and the ARIC Study. JAMA. 1993; 269(4):488–493.
29. Iseki K, Iseki C, Ikemiya Y, Fukiyama K. Risk of developing end-stage renal disease in a cohort of mass screening. Kidney Int. 1996 Mar;49(3):800-5. PubMed PMID: 8648923.
30. Nora Franceschini,1 Kathryn.M. Rose,1 Brad C. Astor,2 David Couper,3 and Suma Vupputuri4.Orthostatic hypotension is associated with incident chronic kidney disease: The Atherosclerosis Risk In Communities Study.Hypertension. 2010 Dec; 56(6): 1054–1059. Published online 2010 Nov 8.
31. Csaba P. Kovesdy, Miklos Z. Molnar, Maria E. Czira, Anna Rudas, Akos Ujszaszi, Laszlo Rosivall, Miklos Szathmari, Adrian Covic, Andras Keszei, Gabriella Beko, Peter Lakatos, Janos Kosa and Istvan Mucsi.Associations between Serum Leptin Level and Bone Turnover in Kidney Transplant Recipients.CJASN December 2010, 5 (12) 2297-2304; DOI: https://doi.org/10.2215/CJN.03520410
32. Andreia Freire de Menezes.Restless Legs Syndrome in Dialysis Patients: Does the Dialysis Modality Influence Its Occurrence and Severity?.Research Article | Open Access Volume 2018 |Article ID 1414568 | 6 pages |
33. Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. Neurology. 2006 Jul 11;67(1):125-30. Review. PubMed PMID: 16832090.
34. La Manna G., Pizza F., Persici E., et al. Restless legs syndrome enhances cardiovascular risk and mortality in patients with end-stage kidney disease undergoing long-term haemodialysis treatment. Nephrology Dialysis Transplantation . 2011;26(6):1976–1983. doi: 10.1093/ndt/gfq681.