DOI: 10.7860/JCDR/2016/22815.8947

Original Article

Internal Medicine Section

A Comparative Study of Neurological Complications in Chronic Kidney Disease with Special Reference to its Stages and Haemodialysis Status

S.G. SHYAM LAKSHMAN[1], P. RAVIKUMAR[2], GIRIDHARI KAR[3], DWIJEN DAS[4], KALLOL BHATTACHARJEE[5], PRITHWIRAJ BHATTACHARJEE[6]

ABSTRACT

Introduction: Globally, Chronic Kidney Disease (CKD) is a critical and rapidly growing health problem and also a major cause of mortality and morbidity. Neurological complications occur in all levels of the nervous system. Central nervous system complications include cerebrovascular accidents, posterior reversible encephalopathy syndrome, osmotic demyelization syndrome, cerebral infection and sinus vein thrombosis. Peripheral nervous system complications include polyneuropathy, mononeuropathy and carpal tunnel syndrome. Haemodialysis (HD) related neurological complications include dialysis disequilibrium syndrome, dementia and cerebrovascular accidents.

Aim: To assess the neurological complications of CKD and to compare the various neurological complications in patients on HD with those not on HD.

Materials and Methods: Hundred patients with CKD were included in the study. They were categorized into two groups according to the stage of CKD and those with stage 3 or more were considered as cases and stage 2 or less as controls. The cases and controls were followed up during subsequent visits for neurological complications.

Results: This study comprised of 50 cases and 50 controls. Among 50 cases, males were 62% and females were 38% with male: female ratio was 1.6:1 and in controls, male: female ratio was 1.08:1. The maximum patients were in the age group of 51-60 years. The incidence of neurological complications was significantly higher in cases compared to controls and among people who underwent dialysis compared to those who were not. Headache was the most common complication both among cases and controls and as well as in people who were on HD. Stroke, seizures and altered sensorium were significantly associated with later stage of CKD. Cases underwent HD had significant association with headache, altered sensorium and stroke than those without HD but peripheral neuropathy and seizure did not show such association.

Conclusion: The chances of development of neurological complications were significantly higher in late stages of CKD compared to early stages of CKD. Those neurological complications were more among people who underwent dialysis when compared to those not on maintenance HD.

Keywords: Dementia, Peripheral nervous system diseases, Renal dialysis, Stroke

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/1.73m^2 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].

Neurological complications include cerebrovascular accidents including Transient Ischemic Attacks (TIA) and stroke. Other complications include Posterior Reversible Encephalopathy Syndrome (PRES), Osmotic Demyelization Syndrome (ODS), cerebral infection, Sinus Vein Thrombosis (SVT). Haemodialysis (HD) related neurological complications include- Dialysis Disequilibrium Syndrome (DDS), headache, dementia and cerebrovascular accidents [3].

Polyneuropathy (PN) is the most common CKD related complication, with prevalence rates of 60% to 100%. This is an insidious chronic length dependent distal sensory motor PN with lower limb involvement more than upper limb involvement [3,4]. Mononeuropathy can occur, especially involving ulnar, median and femoral nerves. The carpal tunnel syndrome is far more common and is caused by entrapment of the median nerve in the carpal tunnel [3].

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 assess the neurological complications of CKD and to compare the various neurological complications in CKD patients undergoing HD with those not on maintenance HD.

MATERIALS AND METHODS

The comparative study was conducted for one year period ranging from 1st June, 2012 to 31st May, 2013 on the patients with CKD who were evaluated and categorized into the respective stages of CKD. The study protocol was approved by the Ethical Committee and written informed consent was obtained from all participants.

Those patients of CKD with stage 3 or more were taken as cases. The cases group was divided into two sub-groups as patients who were on maintenance HD and who were not on HD. Those patients of CKD with less than stage 3 were taken as controls. The cases and controls were selected from patients with CKD having age of 20-80 years. Patients were excluded if they had diabetic nephropathy who have concomitant diabetic neuropathy, CKD due to vasculitis, collagen vascular disorders and amyloidosis which manifests with both Central Nervous System (CNS) and peripheral nervous system complications and CKD with history of alcoholism.

Every 5th case with CKD stage 3 or more on HD or non-HD were included in the study as cases. They were grouped into two namely on HD and non-HD based on whether, they were on HD or not. The total study cases were 50. Every 10th persons admitted in the hospital with CKD of stage 2 or less was taken as controls. The total number of controls was 50.

The cases and controls were observed in the hospital or further followed-up during subsequent visits for neurological complications.

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 m^2:

Stage 0: >90 ml/min/1.73 m^2 with risk factors for CKD

Stage 1: ≥90 ml/min/1.73 m^2 with demonstrated kidney damage

Stage 2: 60-89 ml/min/1.73 m^2

Stage 3: 30-59 ml/min/1.73 m^2

Stage 4: 15-29 ml/min/1.73 m^2

Stage 5: <15 ml/min/1.73 m^2.

Assessment of cognitive status was done by Mini Mental State Examination. Complete blood count, Fasting Blood Sugar (FBS), Post-Prandial Blood Sugar (PPBS), Serum Urea, Creatinine, Serum Protein and Fraction, Serum Electrolytes, Serum Iron Study, Arterial Blood Gas Analysis, Computed Tomography, Magnetic Resonance Imaging, Electro Encephalogram, Nerve Conduction Studies, CSF analysis etc., were done as when necessary.

STATISTICAL ANALYSIS

Collected data were analysed in terms of absolute and relative frequencies of each variable studied by descriptive statistics. Data are presented as the mean ± standard deviation (SD). Statistical significance was calculated for differences between means by unpaired t-test and for observed/expected frequencies; Z-test for difference of proportions was used. For all statistical analyses, a p-value less than 0.05 or Z-value ≥1.96 was considered statistically significant. Analyses were done using Z-test Calculator.

RESULTS

This study was a hospital based comparative study comprising of 50 cases and 50 controls. The 50 cases were further sub-grouped into 27 people who were on maintenance HD and 23 people who were not on HD. Among 50 cases, males were 31 (62%) and females were 19 (38%) with male: female ratio was 1.6:1. Among 50 controls, male: female ratio was 1.08:1 (26:24).

The maximum age incidence in cases and controls was seen in the age group of 51-60 years and 41-50 years respectively [Table/Fig-1].

The most common neurological complications in cases were headache (34%), hemi/paraparesis (24%), sensory symptoms (tingling, paresthesia, numbness) (22%) and in controls were headache (32%), sensory symptoms (14%), hemi/paraparesis (06%) [Table/Fig-2].

Age group (in years)	No. of cases	No. of controls
20-30	02	03
31-40	06	10
41-50	13	13
51-60	21	12
61-70	05	09
71-80	03	03

[Table/Fig-1]: Age distribution in cases and controls.

Neurological Symptoms	Cases	Controls	p-value
Headache	17(34%)	16(32%)	0.833
Hemi/Paraparesis	12(24%)	03(06%)	0.011
Tingling, Paraesthesia, Numbness	11(22%)	07(14%)	0.298
Seizures	07(14%)	01(02%)	0.027
Altered sensorium	07(14%)	01(02%)	0.027
Normal	02(04%)	21(42%)	

[Table/Fig-2]: Neurological complications in CKD patients.

Neurological Symptoms	Haemodialysis (n= 27)	Non-haemodialysis (n = 23)	p-value
Headache	15(55.55%)	02(8.69%)	0.0004
Hemiparesis	08(29.6%)	01(04.3%)	0.020
Altered Sensorium	07(25.92%)	00(00%)	0.008
Tingling, paraesthesia	05(18.51%)	06(26.08%)	0.522
Seizures	04(14.81%)	03(13.04%)	0.857
Paraparesis	01(03.70%)	02(8.69%)	0.459
Normal	00(00%)	02(8.69%)	

[Table/Fig-3]: Neurological complications in CKD patients.

Neuro-radiological Finding	Cases	Controls
Infarct	09(18%)	05(10%)
Haemorrhage	02(04%)	00(00%)
Oedema	04(08%)	00(00%)

[Table/Fig-4]: Different findings of Neuro-radiological imaging in cases and controls.

Nerve conduction study	Cases	Controls
Decreased	08(16%)	03(06%)
Normal	03(06%)	04(08%)

[Table/Fig-5]: Nerve conduction study among cases and controls. p-value=0.109.

In HD group, headache (55.55%), hemiparesis (29.6%) and altered sensorium (25.92%) were most common neurological complications. Sensory symptoms (26.08%), seizures (13.04%), paraparesis and headache (8.69%) were most neurological complications seen in non-HD group [Table/Fig-3].

In the cases group, the neuro-radiological imaging findings were infarct (18%), oedema (8%) and haemorrhage (4%). In contrast to this, infarct (10%) with no finding of oedema and haemorrhage were seen in neuro-radiological imaging of controls [Table/Fig-4].

In Nerve Conduction Study (NCS) among the cases, 16% had decrease in nerve conduction velocity and increased latency and 6% had normal finding but were symptomatic. In the control population, 6% had positive NCS finding and 8% had normal findings [Table/Fig-5].

DISCUSSION

The present study consisting of 50 cases and 50 controls were analysed. The 50 cases were further sub grouped into HD (27 patients) and non-HD (23 patients). The neurological complications

were assessed in cases and control groups and within sub-groups of cases.

In the present study, percentages of cases were 62% males and 38% females with male: female ratio of 1.60:1 with maximum cases in the age group of 51-60 years. In the study conducted by Singh AK et al., 55.1% % were males with male: female ratio of 1.22:1 with mean ± SD age of cases was 45.22 ± 15.2 years [5].

In the present study, headache (34%) was the most common symptom among the cases group and 32% in control group which is in contrast to the study byJesus AC et al., where the incidence of predialysis headache was 76.1% of the patients [6].

Next common symptom was hemiparesis which constituted 24% in cases and 6% in control groups which was statistically significant (p = 0.01174). Koren-Morag N et al., reported that there was 1.54 times more risk of stroke in CKD [7]. Similar observations were found by Chen YC et al., reported that statistically significant (95% CI, 1.45–2.60; p<0.001) in occurrence of hemiparesis in cases group compared to controls [8].

The cases presented with tingling and paraesthesia was 22% compared to 14% in controls. Babu M. Madhusudhana et al., reported that incidence of sensory symptoms were more in end stage renal failure patients than early stages of CKD [9].

Seizures were seen in 14% of cases and 2% of controls which was statistically significant (p = 0.0271) which is comparable to the study of Rizzo MA et al., who reported incidence of seizure in ESRD patients was 10% [3].

In the present study, patients presented with altered sensorium were 14% in cases and among 2% in controls which was statistically significant (p=0.0271). Kurella M and associates reported that there was statistically significant p-value of 0.05 in occurrence of altered sensorium in cases compared to controls respectively [10].

The patients having headache in HD group was 55% compared to control group 8.69% which was statistically significant (p =0.00048). Jesus AC et al., reported incidence of headache in dialysis patients of 46.6% [6].

The patients presented with hemiparesis were 29.6% and 4.3% in HD group and non-HD group respectively (p= 0.02034). Kuo CC et al., study reported significantly higher stroke incidence in the HD cohort than in the control cohort [11].

Altered sensorium was observed in 25.92% cases in HD group in comparison to 0% case in non HD group which was statistically significant (p =0.00854). Kurella M et al., reported similar findings in their studies [10].

Tingling and paresthesia was observed in 18.51% and 26.08% cases in HD and non-HD group respectively (p=0.52218) which is in agreement with the study by Fatima K et al., who reported no significant difference in occurrence of these symptoms and conduction parameters in nerve conduction study among HD patients when compared to non-HD group [12].

In the present series seizures were observed in 14.81% of HD group (4 out of 27 cases) and 13.04% of non HD group (3 out of 23 cases) which was not statistically significant (p =0.85716). Scorza FA et al., study series of 189 patients under dialysis treatment, there was only 3 HD induced seizures [13].

The patients presented with paraparesis probably attributed to myopathy or peripheral neuropathy among the HD group was 3.70% in contrast to 8.69% in non-HD population which was not statistically significant (p =0.4593). Fahal IH et al., study found no significant muscle weakness in HD group [14].

In the cases group, 18% and 4% had cerebral infarct and intra-cerebral haemorrhage in contrast to the control group with 10% and 0% respectively. Oedema was observed in 8% cases and no oedema was present in the control population. Krishna PR et al., observed infarction in 48%, haemorrhage in 40.7% and both infarction and haemorrhage in 11.11% of the patients [15]. Krishna PR et al., reported that reasons for increased incidence of brain infarcts in CKD patients in their study were older patients with multiple risk factors, usage of erythropoietin and (MRI) [15].

In the present series, 16% had positive NCS finding in cases in contrast to 6% in control group (p 0.1096) in the form of reduced nerve conduction velocity and increased latency. In 6% of cases and 8% of control group had symptoms of neuropathy with normal NCS respectively. Santos Adriana Ondina Pestana [16] study reported that there was no significant difference (p=0.402) in occurrence of sensorimotor symptoms with the electrophysiological results in cases group compared to controls.

LIMITATION

As this study comprised of limited numbers of patients, a larger multi-centric study including more number of population for longer duration is required for detailed assessment and definite conclusion.

CONCLUSION

The incidence of neurological complications was significantly higher in late stages of CKD and among people who underwent dialysis when compared to those not on maintenance HD.

Common neurological complications like headache, stroke, seizures, altered sensorium were observed more in advanced CKD than comparison to the early stages and headache, stroke and altered sensorium were seen more in cases underwent HD than those not on HD but peripheral neuropathy and seizure did not show any relationship with HD.

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] Rizzo MA, Frediani F, Granata A, Ravasi B, Cusi D, Gallieni M. Neurological complications of hemodialysis: state of the art. *J Nephrol*. 2012;25(2):170-82.

[4] Krishnan AV, Kiernan MC. Uremic neuropathy: clinical features and new pathophysiological insights. *Muscle and Nerve*. 2007;35(3):273-90.

[5] Singh AK, Farag YM, Mittal BV, Subramanian KK, Reddy SR, Acharya VN, et al. Epidemiology and risk factors of chronic kidney disease in India–results from the SEEK (Screening and Early Evaluation of Kidney Disease) study. *BMC Nephrology*. 2013;14(1):1.

[6] Jesus AC, Oliveira HA, Paixão MO, Fraga TP, Barreto FJ, Valença MM. Clinical description of hemodialysis headache in end-stage renal disease patients. *Arquivos de Neuro-Psiquiatria*. 2009;67(4):978-81.

[7] Koren-Morag N, Goldbourt U, Tanne D. Renal dysfunction and risk of ischemic stroke or TIA in patients with cardiovascular disease. *Neurology*. 2006;67(2):224-28.

[8] Chen YC, Su YC, Lee CC, Huang YS, Hwang SJ. Chronic kidney disease itself is a causal risk factor for stroke beyond traditional cardiovascular risk factors: a nationwide cohort study in Taiwan. *PloS one*. 2012;7(4):e36332.

[9] Babu MM, Kiran MR, Ravindra K, Srinivas V, Kandregula P, Vardhan RV, et al. Clinical manifestation and prevalence of peripheral neuropathy and nerve dysfunction in patients with chronic kidney disease. *International Journal of Research in Medical Sciences*. 2015;3(2):451-55.

[10] Kurella M, Mapes DL, Port FK, Chertow GM. Correlates and outcomes of dementia among dialysis patients: The dialysis outcomes and practice patterns study. *Nephrology Dialysis Transplantation*. 2006;21(9):2543-58.

[11] Kuo CC, Lee CT, Ho SC, Kuo HW, Wu TN, Yang CY. Haemodialysis and the risk of stroke: A population-based cohort study in Taiwan, a country of high incidence of end-stage renal disease. *Nephrology*. 2012;17(3):243-48.

[12] Fatima K, Majid A. Motor nerve conduction studies in patients with chronic renal failure. *Journal of Rawalpindi Medical College (JRMC).* 2010;14(1):11-14.

[13] Scorza FA, Albuquerque MD, Arida RM, Cysneiros RM, Henriques TM, Scorza CA, et al. Seizure occurrence in patients with chronic renal insufficiency in regular hemodialysis program. *Arquivos de neuro-psiquiatria*. 2005;63(3B):757-60.

[14] Fahal IH, Bell GM, Bone JM, Edwards RH. Physiological abnormalities of skeletal muscle in dialysis patients. *Nephrology Dialysis Transplantation.* 1997;12(1):119-27.
[15] Krishna PR, Naresh S, Krishna GS, Lakshmi AY, Vengamma B, Kumar VS. Stroke in chronic kidney disease. *Indian Journal of Nephrology*. 2009;19(1):5.
[16] Santos, Adriana Ondina Pestana. Peripheral neuropathy in patients in haemodialysis treatment. PH.D diss., Universidade da Beira Interior, 2012. http://hdl.handle.net/10400.6/1104.

PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Trainee, Department of General Medicine, Silchar Medical College, Silchar, Assam, India.
2. Postgraduate Trainee, Department of General Medicine, Silchar Medical College, Silchar, Assam, India.
3. Professor, Department of General Medicine, Silchar Medical College, Silchar, Assam, India.
4. Associate Professor, Department of General Medicine, Silchar Medical College, Silchar, Assam, India.
5. Associate Professor, Department of General Medicine, Silchar Medical College, Silchar, Assam, India.
6 Professor and Head, Department of General Medicine, Silchar Medical College, Silchar, Assam, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. P. Ravikumar,
Room.No.14, Old Pg Hostel, Silchar Medical College, Silchar-788014, Assam, India.
E-mail: ravip.nagaraja@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Aug 01, 2016**
Date of Peer Review: **Aug 22, 2016**
Date of Acceptance: **Oct 04, 2016**
Date of Publishing: **Dec 01, 2016**