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RESEARCH ARTICLE

NERVE DYSFUNCTION IN PATIENTS WITHEND STAGE RENAL DISEASE AND CAUSATIVE ROLE OF POTASSIUM-A HOSPITAL BASED STUDY

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is a critical and rapidly growing global health problem. Uremia is considered to be the second leading cause of frequent metabolic neuropathy. Neurological complications occur in almost all patients with severe CKD, potentially affecting all levels of the nervous system, from the CNS through to the PNS. Peripheral neuropathy manifests in almost all such patients, leading to weakness and disability.

Aims and Objectives: To evaluate the changes of Nerve Conduction Velocity in different potassium Value in Chronic Kidney Disease stage 5 and to establish any causal relationship of potassium level with neuropathy in ESRD Patient.

Methodology: Patient admitted with CKD-5 (on Hemodialysis/Not on Hemodialysis) with symptoms of tingling, numbness or feature suggestive of peripheral neuropathy will be randomly selected accordingly inclusion criteria. All epidemiological and clinical data will be recorded. Everybody will be tested for basic investigations including electrolytes in addition to potassium and NCV study. Patients will be divided into three groups- Normokalemic, hypokalemic (potassium<3.5) and hyperkalemic (potassium>5.5). The patients with positive changes of NCV will be tested for any causal relationship with potassium value.

Results: A positive and a highly significant correlation between the level of potassium and neuropathic features in an ESRD patient. A positive association is seen between the NCV changes, mainly axonopathy and demyelination (in long standing cases) and raised potassium levels in ESRD patients. A positive association is seen between potassium level and the stage of neuropathy.

Conclusion: The present study supports the fact that abnormalities in serum potassium constitute a transient homeostatic disturbance which if persistent can lead to more permanent damage to neurons leading to irreversible neuropathy. As far as axons are concerned, regular monitoring and strict control of potassium in the normal range goes very far in the delayed progression of peripheral neuropathy.

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INTRODUCTION

Chronic kidney disease (CKD) is a critical and rapidly growing global health problem. Uraemia is considered to be the second leading cause of frequent metabolic neuropathy .Neurological complications occur in almost all patients with severe CKD, potentially affecting all levels of the nervous system, from the CNS through to the PNS. Peripheral neuropathy manifests in almost all such patients, leading to weakness and disability. 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. [1] A neurologist who is asked to consult on a CKD patient is likely to be faced with several systemic features. The development of clinically relevant neuropathy tends to be a late complication that is typically limited to patients with end-stage kidney disease From a neurological perspective, clinical features of CKD include weakness and length-dependent sensory impairment, which lead to functional disability, and, in patients with acute uremia, an altered mental state due to encephalopathy. Chronic kidney

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disease (CKD) is a rapidly growing global health problem, with a prevalence of 15% in developed nations[2-5]. Chronic kidney disease (CKD) is a global threat to health in general and for developing countries in particular, because therapy is expensive and life-long. The development of uremic neuropathy is exceedingly common in CKD, with prevalence rates of 60-90% in the dialysis population [6,7,8]. Over 1 million people worldwide are alive on dialysis or with a functioning graft . Incidence of CKD has doubled in the last 15 years. In the USA, 30 million people suffer from CKD and by 2010 >600 000 patients will require renal replacement therapy,costing US$28 billion [9].

Aims and Objectives

To evaluate the changes of Nerve Conduction Velocity in different potassium Value in Chronic Kidney Disease stage 5 and to establish any causal relationship of potassium level with neuropathy in ESRD Patient.

MATERIALS AND METHODS

		Materials and Methods
1.	Study area -	Nil Ratan Sircar Medical College and Hospital
2.	Studypopulation-	Indoor Patients in ward of Nil RatanSircar Medical College.
3.	Study period -	January 2013 – July 2014.
4.	Sample size -	80 patients.
5.	Sample design -	Consecutive patients - by simple convenient sampling.
6.	Study design -	Prospective study.

Parameters to be studied

Demographic – Age, Sex, Rural or Urban location, income, education, family history of CKD.

Clinical – Blood pressure (SBP/DBP), Urine output in 24hrs, neuropathy symptoms

Biochemical – Serum urea, serum creatinine and potassium levels(available at central lab), Blood sugar, fasting and Post prandial, Calcium, Phosphate, Uric acid, Urine Routine and Microscopic Examination and culture and sensitivity.

Neurophysiological – Nerve Conduction Velocity studies of both motor and sensory nerves of all four limbs using Recorder Medicare System for NCV study at Neuromedicine in NRSMCH.

Study tools-Detailed history and clinical examination will be done in allpatients, his past records, and blood tests also will berecorded. NCV study will be done in symptomatic patientaccording to protocol at our institution.

Study techniques- Individual patients will be interviewed separately andstudied. Patient admitted with CKD-5 (on Hemodialysis/Not on Hemodialysis) with symptoms of tingling, numbness or feature suggestive of peripheral neuropathy will be randomly selected accordingly inclusion criteria. All epidemiological and clinical data will be recorded. Everybody will be tested for basic investigations including electrolytes in addition to potassium and NCV study. Patients will be divided into three groups-Normokalemic, hypokalemic (potassium<3.5) and hyperkalemic (potassium>5.5). The patients with positive changes of NCV will be tested for any causal relationship with potassium value.

Inclusion Criteria: Patient must be established CKD stage 5 (according to KDIGO/KDOQI guideline) with some symptomatology of peripheral nerve involvement and >18 years. Patient must not have prior dignosed peripheral neuropathy of neurological disorder of other etiology or diabetes which may contribute to neuropathic symptoms. Calcium, sodium and magnesium level must be normal.

Exclusion Criteria: Acute on Chronic Kidney Disease. Peripheral Neuropathy of primary nerve disorder. Acute electrolyte abnormality leading to neuropathy in established End Stage Renal patient.

DISCUSSION

This study is a cross sectional observational study in ESRD patients with symptoms of peripheral neuropathy using inclusion and exclusion criteria. The neuropathy symptoms are graded by the NSS score and the severity of neuropathy (staging) is based on NCV results and NSS score which is taken as T-NSS. The NSS consists of 17 items – 8 focussing on muscle weakness,5 on sensory disturbance and 4 on autonomic symptoms.Items that were answered negative/absent are given a score of zero and present score as one point. Maximum score of 17.The NSS is a validated and widely accepted symptom score for neuropathy [63,64 -66]. All the patients in the present study of 80 patients reported symptoms of neuropathy. The severity of symptoms of neuropathy in the present study was staged as follows using a modified form of a previously devised system (Dyck, 1988). Stage 0, no neuropathy [T-NSS < 2 with normal NCS (nerve conduction study)]; Stage 1, asymptomatic neuropathy (T-NSS = 0 with abnormalities on NCS); Stage 2, symptomatic neuropathy (T-NSS > 2 with normal NCS or T-NSS _ 1 with abnormal NCS; neuropathic symptoms non-disabling); Stage 3, disabling neuropathy (T-NSS >2 with normal NCS or T-NSS _> 1 with abnormal NCS; neuropathic symptoms reported to be disabling.

Discussion about demographic profile

In the present study demographic profiles selectedss are gender, age, religion, residence, education, income and patients on hemodialysis and not on hemodialysis. Out of 80 patients taken, 61% are male and 39% are females. In this study of 80 patients 54% patients are in the 40-59 age group and 20% in the 60-79 age group and 25% in 20-39 age group. The mean age is 48.58 years and SD is 13.68years.P value is < 0.292 which shows no association and ESRD peripheral neuropathy. 61% of symptomatic patients are urban while 39% is rural. P value is 0.94; also bar graph shows ESRD neuropathy distribution almost equal irrespective of residence. In the present study 20% of population is illiterate, 36% went to school and 44% went to college. In the present study, 39% and 40% of the patients are from the lower and higher socioeconomic strata respectively. In this study of 80 patients, 36 of whom are on HD. Out of these 19 are in the 40-59 age group (54%). 45% of HD population is sympyomatic and 55% of non HD is symptomatic. P value is <0.572.Patients on HD can be symptomatic and have their neuropathy attributable to potassium because of post dialysis rebound [54,55].

RESULTS

30% of symptomatic patients are normal NCV;25% have axonal n.23% have radiculopathy with axonal neuropathy ;axonal with demyleinating is 13.75%;7.5% have radiculopathy. Table 9 and pie charts 9(a,b,c) showing axonal with demyleinating and axonal with radiculopathy changes at a score of NSS 1 to 3.The number of the above changes significantly increases with NSS 4 to 6 while NSS score above 8 shows all axonal. Plus at a lower score of 1to 3,24 patients have a normal NCV. Table and diagram 10 shows neuropathy stages with respect to potassium levels.47.5% patients of hyperkalemic patients have stage 3 neuropathy;3% have stage 2 neuropathy.20% of normokalemic patients have stage 0 neuropathy and 20% have stage 2 neuropathy. p value calculated is zero which is highly significant and shows stage 3 neuropathy with hyperkalemic patients. All ESRD patients in the present study of 80 patients reported symptoms of neuropathy. The mean NSS score is 3.125 and SD is 2.17. The mean potassium level of the study group is 5.14 and SD is 1.06.Since sample size is 80 and distribution is normal Pearson's test was applied and a correlation coeeficient of 0.7222 obtained which is highly significant. The R^2 value is 0.5217 which is again highly significant. So this study shows potassium levels having a linear relationship with NSS. Next the distribution of potassium with various types of divided into two groups (1)NCV changes present(axonal neuropathy, demyleinating neuropathy or both) and (2) NCV changes absent (radiculopathy or normal). Radiculopathy per se is not caused by potassium changes. 62.5% patients had positive NCV changes and 37.5% had absent changes in NCV. The mean value and standard deviation of potassium values in both groups were 5.69,0.76 and 4.22,0.85 respectively. Unpaired t-test was applied. The standard error of difference is 0.127 The two-tailed pvalue is less than 0.0001. By conventional criteria, this difference is considered to be extremely statistically significant. So in this study potassium shows strong association with NCV changes[44,45,47,53]. Kiernan MC, Walters RJL, Andersen KV, Taupe D, Murray NMF, Bostock H in their study named Abnormal nerve excitability properties in patients renal failure suggest membrane depolarizalization due to hyperkalemia. Kiernan MC, Bostock H. in their study named Effects of membrane polarization and ischaemia on the excitability properties of human motor axons. Maury E, Lemant J, Dussaule JC, Penicaud Vedrine A, Offenstadt G. in their study named A reversible paralysis. Brain (2005), in his study named Altered motor nerve excitability in end-stage kidney disease128, 2164–2174. In the presents study the association of potassium with neuropathy was explored. Patients were divided into stage 0, stage 2 and stage 3 neuropathy with their respective potassium levels and ANOVA was applied. The mean value of potassium for each stage was calculated. ANOVA analysis shows potassium level in stage 3(K^+=6.03) to be significantly higher than stage 2 (K^+=4.66).p value is <0.001. Although the potassium level of stage 2 falls in the normal range, it is significantly higher than that of stage 0.The f value is 78.145(Tukey HSD post hoc analysis). Next NCV changes distribution was shown with respect to abnormal potassium levels (hyperkalemia and hypokalemia). 48% of NCV (+) were hyperkalemic. p value is 0.006 which is highly significant. ROC curve was obtained for potassium values and NCV changes. The AUC is 0.733 with a lower bound of 0.639 and upper bound of 0.828.The two tailed p value is <0.0001 which is highly significant. This test is fair and strengthens the association between potassium and NCV. Next the correlation of NSS with creatinine was explored. The mean and SD of creatinine were 8.5 and 2.15.The correlation coefficient was -0.00013 which is non significant and shows no association with NSS. So from this it is inferred that a uraemic toxin like creatinines holds a weaker association than potassium with respect to peripheral neuropathy. Next the association of creatinine with Neuropathy stage was shown. The p value is 0.572 which is non significant and proves no association between the two[53].

The correlation of creatinine clearance with NSS is also non significant with a coefficient of -0.11. The present study is a cross sectional study in ESRD patients with symptoms of peripheral neuropathy where data has been taken from patients admitted in the medicine ward of NRS Medical College and Hospital. Neuropathy symptoms were graded according to NSS score, NCV results were obtained and patients were staged into three groups according to the stage of neuropathy-stage 0, stage 2 and stage 3.

Table 1. Age HD Distribution

AGE	HD				Total	%
	Yes	Yes %	No	No %		
20-39	11	14	9	11	20	25
40-59	19	24	24	30	43	54
60-79	6	8	10	13	16	20
>80	0	0	1	1	1	1
TOTAL	36	45	44	55	80	100

Table 2. NCV change distribution in sample

NCV	AXONAL	DEMYLEINATIG	RADICULOPATHY	Normal	AXONAL + DEMYLEINATIG	DEMYLEINATIG+ RADICULOPATHY	RADICULOPATHY+ AXONAL	Total
	20	0	6	24	11	0	19	80
%	25	0	7.5	30	13.75	0	23.75	100

Table 3. K+ in HD and non HD patients

K+	HD				Total	Total %
	Yes	Yes %	No	No %		
Hypokalemic (<3.5)	6	7.5	1	1.25	7	9
Normokalemic (3.5-5.5)	16	20	16	20	32	40
Hyperkalemic (5.5>)	14	17.5	27	33.75	41	51
Total	36	45	44	55	80	100

CHI-SQUARE VALUE	FREEDOM OF DISTRIBUTION	P-VALUE
6.963	2	0.03

Table 4. NCV result distribution at different NSS levels

NSS	NCV							Total Number of Patients
	AXONALSM	DEMYLEINATIG	RADICULOPATHY	Normal	AXONAL + DEMYLEINATIG	DEMYLEINATIG+ RADICULOPATHY	RADICULOPATHY+ AXONAL	
1 To 3	10		3	24	3		8	48
4 To 6	8		3		8		11	30
8 and Above	2							2

Table 5. K+ with NCV stage

K+	NCV						Total
	Stage 0	Stage 0 %	Stage 2	Stage 2 %	Stage 3	Stage 3 %	
Hypokalemic (<3.5)	7	8.75		0		0	7
Normokalemic (3.5-5.5)	16	20	16	20		0	32
Hyperkalemic (5.5>)			3	3.75	38	47.5	41
Total	23	28.75	19	23.75	38	47.5	80

Table 6. K+ Level with NCV

K+	NCV							Total Number of Patients
	AXONALSM	DEMYLEINATIG	RADICULOPATHY	Normal	AXONAL + DEMYLEINATIG	DEMYLEINATIG+ RADICULOPATHY	RADICULOPATHY+ AXONAL	
Hypokalemic (<3.5)	0	0	3	4	0	0	0	7
Normokalemic (3.5-5.5)	7	0	0	20	0	0	5	32
Hyperkalemic (5.5>)	14	0	3	0	11	0	13	41

Correlation	0.722266

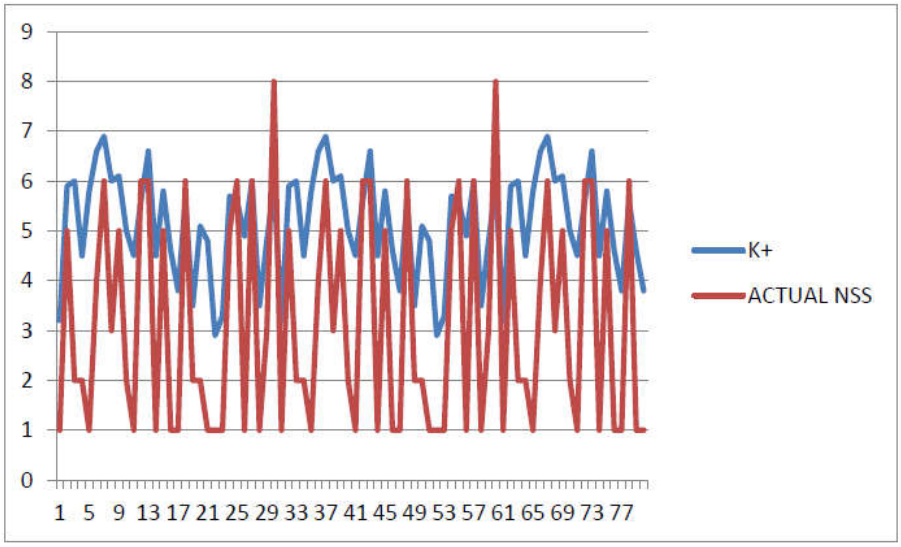

Figure 1. K+ with NSS score

Table 7. NCV changes with respect to abnormal K+ level

	NCV Changes + (Axonal/ DEMYLEINATIG or Both)	NCV Changes + (Axonal /DEMYLEINATIG or Both) %	NCV Changes - (Radiculopathy or Normal)	NCV Changes - (Radiculopathy or Normal) %	Total	%
Hypokalemic (<3.5)	0	0	7	15	7	15
Hyperkalemic (5.5>)	23	48	18	38	41	85

Sample was divided into NCV(+) and NCV(-).48% of NCV (+) were hyperkalemic.p value is 0.006 which is highly significant.

CHI-SQUARE VALUE	FREEDOM OF DISTRIBUTION	P-VALUE
7.54	1	0.006

Demographic data relating to gender, age, residential area, education, income and whether the patients are on HD or not which have largely proved inconclusive and insignificant with respect to the present study. In exploring the relationship between potassium and peripheral neuropathy symptoms, a positive correlation between potassium and neuropathy symptoms was found.

1) A positive and a highly significant correlation between the level of potassium and neuropathic features in an ESRD patient.
2) A positive association is seen between the NCV changes, mainly axonopathy and demyelination (in long standing cases) and raised potassium levels in ESRD patients.
3) A positive association is seen between potassium level and the stage of neuropathy.

The present study supports the fact that abnormalities in serum potassium constitute a transient homeostatic disturbance which if persistent can lead to more permanent damage to neurons leading to irreversible neuropathy. As far as axons are concerned, regular monitoring and strict control of potassium in the normal range goes very far in the delayed progression of peripheral neuropathy.

Summary and Conclusion

The present study is a cross sectional study in ESRD patients with symptoms of peripheral neuropathy where data has been taken from patients admitted in the medicine ward of NRS Medical College and Hospital. Neuropathy symptoms were graded according to NSS score, NCV results were obtained and patients were staged into three groups according to the stage of neuropathy-stage 0, stage 2 and stage 3. Demographic data relating to gender, age, residential area, education, income and whether the patients are on HD or not which have largely proved inconclusive and insignificant with respect to the present study. In exploring the relationship between potassium and peripheral neuropathy symptoms, a positive correlation

between potassium and neuropathy symptoms was found. A positive and a highly significant correlation between the level of potassium and neuropathic features in an ESRD patient. A positive association is seen between the NCV changes, mainly axonopathy and demyelination (in long standing cases) and raised potassium levels in ESRD patients. A positive association is seen between potassium level and the stage of neuropathy. The present study supports the fact that abnormalities in serum potassium constitute a transient homeostatic disturbance which if persistent can lead to more permanent damage to neurons leading to irreversible neuropathy. As far as axons are concerned, regular monitoring and strict control of potassium in the normal range goes very far in the delayed progression of peripheral neuropathy.

REFERENCES

1. Mallick, N. P & Gokal, R. Haemodialysis. *Lancet,* 353, 737-742 (1999).
2. Chadban, S. J. *et al*. Prevalence of kidney damage in Australian adults: the AusDiab kidney study. *J. Am. Soc. Nephrol*., 14, S131-S138 (2003).
3. Fox, C. S. *et al*. Cross-sectional association of kidney function with valvular and annular calcification: the Framingham heart study. *J. Am. Soc. Nephrol*., 17, 521-527 (2006).
4. Nitsch, D. *et al*. Prevalence of renal impairment and its association with cardiovascular risk factors in a general population: results of the Swiss SAPALDIA study. *Nephrol. Dial. Transplant*., 21, 935-944 (2006).
5. Ninomiya, T. *et al*. Chronic kidney disease and cardiovascular disease in a general Japanese population: the Hisayama Study. *Kidney Int*., 68, 228-236 (2005).
6. Angus-Leppan, H. & Burke, D. The function of large and small nerve fibers in renal failure. *Muscle Nerve*, 15, 288-294 (1992).
7. Krishnan, A. V. *et al*. Altered motor nerve excitability in end-stage kidney disease. *Brain*, 128, 2164-2174 (2005).
8. Laaksonen, S., Metsarinne, K., Voipio-Pulkki, L. M. & Falck, B. Neurophysiologic parameters and symptoms in chronic renal failure. *Muscle Nerve*, 25, 884-890 (2002).
9. Campise M, Bamonti F, Novembrino C *et al*. Oxidative stress in kidney transplant patients. *Transplantation*, 2003; 76: 1474–1478
10. (Raskin and Fishman 1976a; 1976b)
11. Aminoff MJ. In: Raskin NH, editor. Neurology and general medicine. Philadelphia: Churchill Livingstone; 1995. p. 303–19.
12. Galassi G, Ferrari S, Cobelli M, Rizzuto N. Neuromuscular complications of kidney diseases. Nephrol Dial Transplant 1998;13(Suppl7):41–7.
13. Dumitru D, Amato A, Zwarts M. Electrodiagnostic Medicine. Philadelphia: Hanley & Belfus; 2002 (pp. 984–986).
14. International Journal of Genetics and Molecular Biology Vol. 3(11), pp. 155-160, December 2012 Available online at http://www.academicjournals.org/,IJGMB ISSN2006-9863 ©2012 Academic Journals, DOI: 10.5897/IJGMB 11.022 Uraemic neuropathy: A review Basilio Vagner Ramírez 1,2* and Paula Andrea Bustamante Gómez3
15. Kusakari J, Kobyashi T, Rokugmo M, *et al*. The inner ear dysfunction in hemodialysis patients: *Tohuku J Exp Med*., 1981;135:359-69.
16. Kersh ES, Kronfield SJ. Unger A, Popper RW, Cantor S, Cohn K. Autoimmune insufficiency in uraemia as a cause of hemodialysis induced hypotension. *N Engl J Med*., 1971;290:650-3.
17. Spencer PS, Schaumberg HH. Central peripheral distal Axonopahies pathology of 'dying-back' polyneuropathies, *Prog Neuropath*., 1977;3:255-95.
18. Schaumberg HH,Spencer PS. Toxic Neuropathies. *Neurology*, 1979;29:429-31.
19. Raskin NH, Fishman RA. Neurological disorders in renal failure. *N Engl J Med*., 1976;294:143-8;204-IO.
20. Teschan PE, Ginn HE, Bourne JR, *et al*. Quantitative indices of clinical uraemia. *Kidney Int*., 1979;15:676-97.
21. Nielsen VK. The peripheral nerve function in chronic renal failure a survey. *Acta Med Scand*., 1974;196:7-32.
22. Asbury AK.Uraemic Neuropathy.In Dyck PJ,Thomas PK, Lambert EH,eds. peripheral neuropathy. v 2.W B Saunders, Co.:Philadelphia;1975:982-92.
23. Nielsen VK.The peripheral nerve function in chronic renal failure.VI The relationship between sensory and motor nerve conduction and kidney function,azotemia,age,sex and clinical neuropathy.Acta Med Scand.1973;195:455-62.
24. Dyck PJ, Johnson WJ, Lambert EH, O'Brien PC. Sesmental demyelination secondary to axonal degeneration in uraemic polyneuropathy. *Mayo Clini Proc*., 1971;46:400-31.
25. Fraser CL, Arieff AI. Nervous system manifestation of renal failure. 1988; 28:3063-92
26. Asbury AK. Recovery from uremic neuropathy. *N Engl J Med*., May 27 1971;284(21):1211-2. [Medline].
27. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Bostock H, Kiernan MC. Altered motor nerve excitability in end-stage kidney disease. *Brain*. 2005;128:2164-74.
28. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Kiernan MC. Sensory nerve excitability and neuropathy in end stage kidney disease. *J Neurol Neurosurg Psychiatry*. 2006;77:548-51.
29. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Bostock H, Kiernan MC. Neuropathy, axonal Na+/K+ pump function and activity-dependent excitability changes in end-stage kidney disease. *Clin Neurophysiol*., 2006;117:992-9.s
30. Lonergan ET,Semar M,Sterrzel EB,*et al*.,Erythrocyte transketolase activity in hemodialyzed patients:a reversible metabolic lesion in uraemia.N Engl J Med.1971;284:1399-403.
31. Giovanetti S, Balestri PL, Barsotti G. Methylguanidine in uraemia. *Arch Intern Med*.,1973;131:709-13.
32. Reznek RH, Salway JG, Thomas PK. Plasma myoinositol concentration in uraemic neuropathy. *Lancet*, 1977;1:675-6.
33. Scribner BH. Discussion. *Trans Am Soc Artif Intern Org.,* 1965; 11: 29
34. Babb AL, Ahmad S, Bergström J, Scribner BH. The middle molecule hypothesis in perspective. *Am J Kidney Dis.,* 1981; 1: 46–50
35. Jones NF, Poston, L. Disorders of potassium metabolism. In: Cohen RD, Lewis B, Alberti KGMM, Denman AM, eds. The Metabolic and Molecular Basis of Acquired Disease. Baillère Tindall, London; 1990: 1070–1095.
36. Ledingham JGG. Disorders of potassium metabolism. In: Weatherall DG, Ledingham JGG, Warrell DA, eds. Oxford Textbook of Medicine. Oxford University Press, Oxford; 1996: 3127– 3135.
37. Halperin ML, Kamel KS. Potassium. *Lancet*, 1998; 352: 135–140.
38. Charytan D, Goldfarb DS. Indications for hospitalisation of patients with hyperkalemia. *Arch Intern Med*., 2000; 160: 1605–1611.

39. (39) Stys PK, Ransom BR, Black JA, Waxman SG. Anoxic/ischemic injury in axons. In: Waxman SG, Kocsis JD, Stys PK, eds. The Axon. Oxford University Press, NewYork;1995: 462–479
40. Nielsen VK. The peripheral nerve function in chronic renal failure. V. Sensory and motor conduction velocity. *Acta Med Scand*., 1973; 194: 445–454.
41. Bolton CF, Young GB. Neurological Complications of Renal Disease. Butterworths, Boston; 1990.
42. Hanicki Z. Middle molecules, myth or reality? *Mater Med Pol.,* 1985; 17: 51–55.
43. Massry SG. Current status of the role of parathyroid hormones in uremic toxicity. *Contrib Nephrol*., 1985; 49: 1–11.
44. Kiernan MC, Walters RJL, Andersen KV, Taupe D, Murray NMF, Bostock H. Abnormal nerve excitability properties in patients with renal failure suggest membrane depolarization due to hyperkalemia. *Brain*, 2002; 125: 1366–1378.
45. Kiernan MC, Bostock H. Effects of membrane polarization and ischaemia on the excitability properties of human motor axons. *Brain,* 2000; 123: 2542–2551.
46. Kuwabara S, Kanai K, Sung J-Y *et al*. Axonal hyperpolarization associated with acute hypokalemia: multiple excitability measurements as indicators of the membrane potential of human axons. *Muscle Nerve*, 2002; 26: 283–287.
47. Maury E, Lemant J, Dussaule JC, Penicaud Vedrine A, Offenstadt G. A reversible paralysis. *Lancet*, 2002; 360: 1660.
48. Navarro J. The biochemical basis of the uraemic syndrome. In: Cohen RD, Lewis B, Alberti KGMM, Denman AM, eds. The Metabolic and Molecular Basis of Acquired Disease. Baillère Tindall, London; 1990: 1280–1293
49. De Deyn PP, D'Hooge R, Van Bogaert PP, Marescau B. Endogenous guanidine compounds as uraemic neurotoxins. *Kidney Int Suppl*., 2001; 78: S77–S83
50. De Deyn PP, Vanholder R, D'Hooge R. Nitric oxide in uraemia: effects of several potentially toxic guanidine compounds. *Kidney Int Suppl*., 2003; 84: S25–S28
51. Vanholder R, De Smet R, Glorieux G *et al*. Review on uremic toxins: classification, concentration, and interindividual variability. *Kidney Int*., 2003; 63:1934–1943
52. Schaumburg HH, Berger AR, Thomas PK. Uremic neuropathy. In: Disorders of peripheral nerves. 2nd ed. Philadelphia: FA Davis, 1992:156–63.
53. Brain (2005), Altered motor nerve excitability in end-stage kidney disease, 128, 2164–2174
54. Ahmed J, Weisberg LS. Hyperkalemia in dialysis patients. *Semin Dial*., 2001; 14: 348–56.
55. De Nicola L, Bellizzi V, Minutolo R, Cioffi M, Giannattasio P, Terracciano V, *et al*. Effect of dialysate sodium concentration on interdialytic increase of potassium. *J Am Soc Nephrol*., 2000; 11: 2337–43.

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