Original Research Paper

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Nephrology

A STUDY OF PERIPHERAL NEUROPATHY IN CHRONIC KIDNEY DISEASE STAGE -5 AND IT'S OUTCOME AFTER KIDNEY TRANSPLANTATION

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ABSTRACT Peripheral neuropathy is common in Chronic kidney disease (CKD) patients on Hemodialysis . It may be overt or subclinical. Neuropathic symptoms & signs may not improve with Hemodialysis. However a successful kidney Transplantation may revert / improve most of the symptoms and signs of Peripheral Neuropathy in CKD patients .In this Study we have compared the clinical &Electrophysiologic parameter's in the Pre-transplant & Post Transplant period . We found a statistically significant improvement in Neuropathy in the Post-Transplant period ..

KEYWORDS : CKD,ESRD,Neuropathy ,Nerve conduction study, Amplitude, Conduction velocity,Distal latency, SNAP,CMAP.

INTRODUCTION

Neurological complications occur in approximately 60% of patients suffering from severe Chronic Kidney Disease (CKD), affecting the nervous system at all levels, central as well as peripheral, yielding weakness, prolonged disability and alteration of mental state[1,2]. Amongst the many manifestations of uraemia, the most common is uraemic neuropathy and its prevalence increases as Glomerular filtration rate (GFR) decreases and also depends on the duration of the CKD and dialysis therapy.Its prevalence is about 60- 100%[3] in those on dialysis.Even though many patients may not have overt symptoms or signs, electro-physiological abnormalities in Nerve conduction studies(NCS) may be detected in many patients indicating the presence of subclinical neuropathy. Uraemic neuropathy characteristically progresses over the course of months, but can occasionally take a faster course, triggering a marked disability . It is believed that Uraemic neuropathy is caused by the accumulation of medium-sized molecules that have not been adequately filtered.Even though regular maintenance Hemodialysis(HD) slows the progression of neuropathy, the abnormalities rarely improve or sometimes they may worsen.However renal transplantation is associated with rapid improvement in these neuro-physiological abnormalities within days and clinical improvement over months[5]

Aim of the study

This study aims to evaluate the prevalence of peripheral neuropathy(both overt and subclinical) in CKD stage -5 patients on HD (particularly those on transplant programme) through Nerve conduction studies(NCS) and to assess the outcome of neuropathy after renal transplantation by follow-up NCS at the end of first and third months post Renal transplantation.

Materials and Methods

This study was conducted from August 2010 to December 2011 at Department of Nephrology, Madras Medical college and Rajiv Gandhi Government General Hospital, Chennai with active support from Neurology Department.The study protocol was approved by the Ethics Committee of the Government General Hospital and all subjects gave their informed consent prior to the study.

Inclusion criteria

The study included 35 CKD stage V patients on Maintenance HD(polysulfonedialyser, low flux) who were on Kidney transplantation programme(Live related) in our department.

Exclusion criteria

Diabetes mellitus ,small vessel vasculitis,SLE,Chronic alcoholic

Methodology

All participants were assessed for the presence of peripheral neuropathy by eliciting detailed history regarding symptoms of neuropathy, co-morbid illness history of alcohol intake, drug intake ,duration of CKD and period of Hemodialysis(HD).Detailed neurological examination was performed to assess presence of decreased touch , pain ,temperature, vibration and position sensations and motor abnormalities like decreased power and deep tendon reflexes(DTR) in the extremities. Routine investigation include urine analysis, complete hemogram, Blood Urea, serum creatinine ,Electrolytes,Liver function tests ,Viral Markers and thyroid function tests.All these patients were on supplemental doses of vitamin B complex during the period of study.All patients were subjected to Nerve conduction studies (motor and sensory of both upper and lower limbs). It was done immediately after a HD session so that patients were oedemafree .

Electrodiagnostic Measures-Standardization

TheElectro diagnostic protocol, as recommended by AAEM was used.Neuro-physiological studies were performed by RECORDERS and MEDICARE SYSTEMS EMG. EP MARK – II, EMG machine, a 4channel electrophysiological device.Recommended filter settings (approximate values) were 20-3,000 Hz band-pass for sensory studies, 2-10,000 Hz band-pass for motor studiesThe temperature of the room was maintained at 22-24oC during all processes.Standardized nerve conduction techniques were used. Conventional methods using surface electrodes for motor conduction and ring electrodes for sensory conduction were used

NCS IN THE LOWER LIMBS .

In the lower limbs sensory conduction in suralnerve(**SNAP**- ***sensory nerve action potential)*** and motor conductions in tibial nerves(**CMAP**-Compound Muscle action potential) were done bilaterally in all the patients.

NCS IN UPPER LIMBS

Nerve conduction studies in the upper limbs included sensory(**SNAP**) and motor(**CMAP**) conductions of median nerve. The Median nerve NCS study was done in the non AV fistula arm and in those patients who did not have an AVF it was done on the dominant arm (Right).None of the patients had symptoms or signs of carpal tunnel syndrome.

COMPONENTS ASSESSED:

Distal Latency (DL),Proximal latency(PL),,Amplitude(Amp),Nerve conduction velocity **(NCV)**

The following parameters were measured

Sural nerve- Amplitude, CV, DL of **SNAP**

Tibial nerve- Amplitude, CV, DL of ***CMAP***

Median nerve- Amplitude, CV, DL of ***SNAP and CMAP***

Protocol for electrodiagnostic test:

The normal values for representative nerve conduction values at

various sites of stimulation were derived at after analyzing the NCS of 20 age matched patients who came to Neurology OPD for complaints other than neuropathy.**Normal values**

Sensory nerve conduction studies(SNAP)

Nerve	Amplitude(mv)	CV(m/s)	Distal Latency (ms)
Sural	>6	>40	<4.4
Median	>5	>50	<3.5

Motor nerve conduction studies© MAP)

Nerve	Amplitude (mv)	CV(m/s)	Distal Latency(ms)	F wave latency(ms)
Median	>4.2	>49	<4.2	<30
Tibial	>4.1	>41	<6	<56

Based on the results the patients were divided into two groups

Group 1- patients who had clinical or electrophysiological evidence of neuropathy

Group 2- patients who had no clinical or electrophysiological evidence of Neuropathy

The parameters(SNAP,CMAP) were analyzed to assess whether it's a **axonopathic** (↓ amplitude, ↔ conduction velocities , ↔ distal latency) or **demyelinating**(normal amplitude, ↓ CV ,↑ Latency) They were further divided into predominantly ***sensory , motor or mixed sensorimotor*** involvement or predominant lowerlimb or upperlimb or involvement of both limbs. Those patients in group 1 who had clinical or Neuro-physiological evidence of neuropathy underwent follow-up NCS in Post renal transplant period at the end of 1st and 3rd months. The parameters mentioned above were measured again and the results were compared with the pre-transplant values and analyzed for statitistical significance.**Statistical analysis** was done using SPSS software using repeated measures ANOVA test .

RESULTS

The study included 35 participants(CKD Stage 5 patients) on Hemodialysis(HD) and on live related kidney transplantation programme. 30 patients(24 males;6 females) completed the study.(5 people had either died or lost to follow up)

Native kidney disease among participants

	Male	Female
Chronic Glomerulonephritis	8	3
Chronic Interstitial nephritis	4	
CAKUT		1
Not known	12	1
Acute cortical necrosis		1

Pre-tranplant clinical examination:

Of the thirty patients , 8 (26.6%)(7M:1F) had clinical evidence of peripheral neuropathy. The main symptoms were paresthesiae or dysesthesiae of feet (burning sensation , tingling, pins and needles, or cramp-like sensations) and or numbness. On neurologic examination these patients had symmetrical decreased vibration sense in the toes and ankle and also ↓temperature and superficial pain sensations in the feet. Six (20%) patients had decreased ankle jerk.None of them had restless leg syndrome, weakness, wasting, spontaneous disabling pain in the limbs or sensory ataxia. All 30 underwent **NCS** in the pretransplant period . On NCS 20(66.7%) patients showed evidence of peripheral neuropathy.{8 symptomatic and 12 asymptomatic patients(subclinical neuropathy)}.

Fig 1.***Sex ratio of patients***

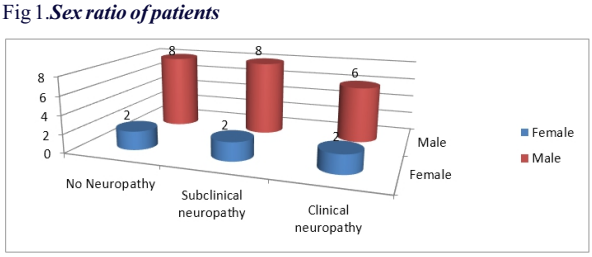


Fig 2-Influence of duration of CKD and of dialysis on neuropathy

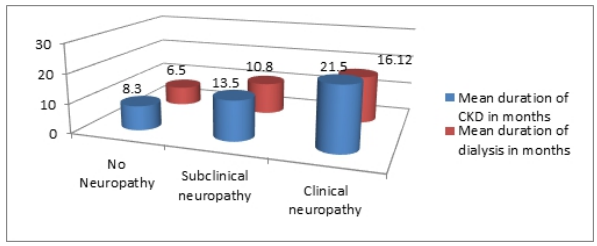
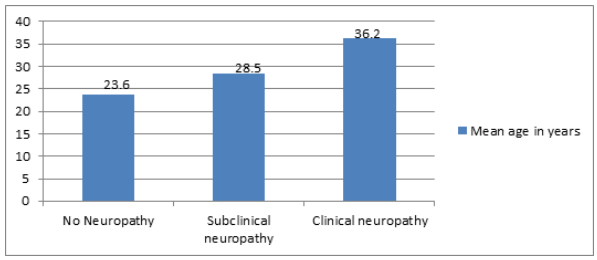


Fig.3-Mean age in years of patients & status of neuropathy



Tab 2-Clinical profile

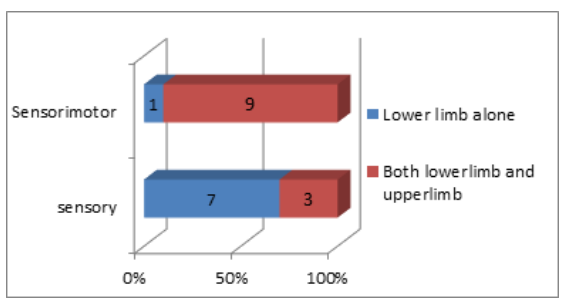
All 20 patients who had clinical or subclinical neuropathy underwent repeat NCS after successful renal transplantation at the end of 1st and 3rd months

Parameter	No neuropathy	SubClinical neuropathy	Clinical neuropathy
No	10	12	8
M:F	8:2	10:2	6:2
Mean age in years	23.6	28.5	36.2
Mean duration of CKD in months	8.3	13.5	21.5
Mean duration of dialysis in months	6.5	10.8	16.12
HCV	2	1	

Tab.3 Results of NCS

Neuropathy	sensory	Sensorimotor
Lower limb alone	7	1
Both lowerlimb and upperlimb	3	9

Fig4. Pattern of neuropathy



Tab.4-NCS OF RIGHT SURAL NERVE(SENSORY NERVE ACTION POTENTIAL)

Parameter	PRE TX (A)	POST TX 1 month (B)	p value A vs B	POST TX 3 month (C)	p value A vs C	p value B vs C	n
Distal latency ms mean(sd)	3.570 (0.71)	2.963 (0.6562)	>.05	2.527 (0.4776)	<.05	>.05	16
Amplitude in mv mean (sd)	4.831 (0.7846)	5.913 (1.060)	<.05	7.213 (1.244)	<.05	>.05	
conductio n velocity mean(sd)	38.275 (1.541)	46.758 (4.715)	<.05	54.217 (8.220)	<.05	>.05	

The suralnerve SNAP was obtained successfully in 26 subjects (86.6%). 16/26(61.53%) patients had abnormal SNAP in the pretransplant period. Follow-up results of these 16 patients were analysed.In 4(13.3%) patients sural nerve SNAP was absent bilaterally in Pre- transplant period.,but were included in the follow-up study

Table. 5 Left- SURAL NERVE SNAP

Parameter	PRE TX (A)	POST TX 1 month (B)	p value A vs B	POST TX 3 months (C)	p value A vs C	p value B vs C	n
Distal latency in ms mean (SD)	3.606 (1.056)	3.136 (1.470)	>.05	2.528 (0.5468)	<.05	>.05	16
Amplitude in mv mean(SD)	5.188 (0.447)	5.981 (0.7195)	<.05	7.057 (1.058)	<.05	<.05	
conduction velocity mean(SD)	38.350 (1.637)	46.874 (3.741)	<.05	54.706 (4.820)	<.05	>.05	

In the transplant NCS 61.43% had involvement of sural nerve bilaterally.It was associated with ↓ amplitude of SNAP,↓ or↔ Conduction velocity and a near normal distal latency(an axonopathic pattern).. The follow up study showed there is increase in SNAP, conduction velocity,Amplitude of sural nerves bilaterally.

Table 6-Right TIBIAL NERVE CMAP

The Righttibial nerve CMAP was obtained successfully in all the patients.10 patients had abnormalities in pre-transplant CMAP of tibial nerve bilaterally of axonopathic type. Follow-up data were analyzed for these ten patients and compared

Parameter	Pre tx (A)	post t x 1 mon (B)	p value A vs B	post tx 3 mon (C)	p value A vs C	p value B vs C	n
Distal latency ms mean(sd)	4.050 (1.70)	3.722 (0.5842)	>.05	3.323 0.7278	>.05	>.05	10
Amplitude in mv mean(sd)	3.690 (0.3213)	4.320 (0.6630)	>.05	5.150 (0.9277)	<.05	<.05	
Conduction velocity m/s mean(sd)	42.344 (5.449)	47.079 (5.605)	>.05	48.890 (3.816)	<.05	>.05	

Tab.7 - Left -TIBIAL NERVE CMAP

The same 10 patients had abnormalities in pre-transplant CMAP of of left tibial nerve. These data show there is significant increase in CV and amplitude and a non-significant decrease in distal latency.

Parameter	Pre tx (A)	Post tx 1 month (B)	p value A vs B	Post tx 3 months (C)	p value A vs C	p value B vs C	n
Distal latency ms mean (sd)	3.689 (1.204)	3.613 (0.5815)	>.05	3.066 (0.6917)	>.05	>.05	10
Amplitude in mv mean(sd)	3.820 (0.193 2)	4.3 (0.6498)	>.05	5.270 (1.197)	<.05	<.05	
conduction velocity mean(sd)	40.1 (1.897)	47.938 (5.104)	<.05	49.212 (4.955)	<.05	>.05	

Tab.8-MEDIAN NERVE SNAP

11 patients had abnormal NCS in median nerve SNAP values in the pre-transplant period. It showed ↓ amplitude, ↔ conduction velocities , ↔ distal latency. Follow-up data of these 11 patients analyzed.It was associated with improvement in electrophysiology (↑ in CV and amplitude).

Parameter	Pre tx (A)	Post t x 1 month (B)	p value A vs Bb	Post tx 3 mon (C)	p value A vs C	p value B vs C	N
Distal latency ms mean(sd)	2.073 (0.5176)	1.994 (0.3525)	>.05	2.132 (0.4039)	>.05	>.05	11
Amplitude in mv mean(sd)	4.636 (0.3802)	5.318 (0.3430)	<.05	6.264 (0.6562)	<.05	>.05	
Conduction velocity mean(sd)	48.351 (2.729)	59.653 (5.051)	<.05	64.784 (5.041)	<.05	>.05	

Tab.9-MEDIAN NERVE CMAP

6 patients had abnormal NCS in Median nerve CMAP values in the pre-transplant period. Follow-up data of these 6patients analyzed. It also showed increased amplitude , CV & decreased latency in the post –transplant period.

Parameter	pre tx (A)	post t x 1 mon (B)	p value A vs B	post tx 3 mon (C)	p value A vs C	p value B vs C	N
Distal latency ms mean (sd)	3.098 (0.7223)	2.915 (0.3122)	>.05	2.892 (0.3158)	>.05	>.05	6
Amplitude in mv mean (sd)	4.0 (0.0894)	4.383 (0.2483)	<.05	5.833 (0.3724)	<.05	>.05	
conduction velocity m/s mean (sd)	51.605 (3.837)	55.563 (5.169)	>.05	61.358 (6.399)	<.05	>.05	

The same 10 patients had abnormalities in pre-transplant CMA of left tibial nerve.These data show there is significant increase in CV and amplitude and a non-significant decrease in distal latency

DISCUSSION

In this study of 30 patients ,only 8 had symptoms / signs of peripheral neuropathy(overt) where another 12 had NCS evidence of neuropathy (subclinical).The clinical neuropathy group is associated with relatively older age(36.2 vs28.5y) longer period of CKD(21.5 vs 13.5 m) and dialysis(16.1vs 10.8m).Those patients in group 1(neuropathic) had only relatively mild symptoms and signs when compared to earlier studies .This could be to initiation of Renal Replacement Therapy(RRT) earlier ,shorter duration of dialysis and earlier kidney transplantation. None of the patients in our cohort had restless leg syndrome.This is in discordance with earlier literature (Ekbom KA et al),which show it was very common in among dialysis patients. This may be due to shorter period of dialysis and CKD in our cohort which may account for the lower incidence.One patient in group 1 had Hepatitis C infection in the pretransplant period . However his Serum cryoglobulin was negative.

SENSORY NERVE ACTION POTENTIAL(SNAP) STUDY

In the pretransplant NCS 61.43% had involvement of sural nerve bilaterally.It was associated with ↓ amplitude of SNAP,↓ or↔ Conduction velocity and a near normal distal latency(an axonopathicpattern).In 4(13.3%) patients sural nerve SNAP was absent bilaterally in pretransplantperiod.It is possible that the inability to record a distal sural SAP with surface electrodes may represent early changes of an as yet subclinical neuropathy,or it resulted from the difficulty in distinguishing a low amplitude SAP from noise.However the nerves could be stimulated in the post transplant period and the neurophysiological parameters(↑ amplitude,↑ Conduction velocity) improved between the two NCS done in the post transplantperiod. Hence it was most likely due to neuropathic involvement. .Of all lower limb sensory nerves only the sural provides such a ready index of lower limb sensory function. Sensory conduction studies in lower limb nerves have a higher percentage yield in polyneuropathy than such studies in upper limb nerves in concordance with Davidburke,et al[35].Post transplant studies in sural nerve SNAP showed increasing

amplitudes and CV between pretransplant and post transplant 3 months values(p <.05).In the upperlimb SNAP of Median nerve showed axonal type of involvement in 11 (36.6%) patients. Its is associated with CMAP abnormalities in 6(20%) patients. Following transplant there is there is an ↑ in amplitude and CV between 0 and 3 months(p<.05) .

MOTOR NERVE CONDUCTION STUDIES

Tibial and median nerves CMAP showed abnormalities of axonopathic type in 10(33.3%)and 6(20%) patients, respectively.These patients also had associated sensory nerve involvement. Post transplant there is an improvement in neuro-physiological parameters with increase in amplitude , CV and decrease in latency(ns).one of the patients had motor nerve involvement without sensoryinvolvement.Our study correlates with earlier studies in that involvement in uremic neuropathy is a "dying back " axonal [1,2]neuropathy with distal symmetrical involvement and length-dependent polyneuropathy,in which the it is that the neurons that have the longest axons appear to be the first to be affected similar to that what was observed. by DyckPJ,et al[3].It also concords that there is predominant sensory involvement, with lower limb involved much more than upperlimb as have been described by Spencer and Schaumberg et al[4].The earlier electrophysiological improvement seen in CV and amplitude (CV>Amplitude) may be due to segmental remyelination followed by axonal recovery suggested as by Bolton, C. F.,et al[5].The almost invariable improvement of neuropathy after transplantation is due to clearance of " Middle molecules" such as methyl guanidine and myoinositol, which has been shown to correlate with the degree of neurotoxicity . These toxins (and the clinical signs of neuropathy) are not greatly reduced by hemodialysis.The most commonly affected parameter in the present study was sural SNAP amplitude, which was abnormal in a higher percentage of patients than median SNAP amplitude,consistent with the lower limb predisposition of neuropathy similar to the study *by* Arun V. Krishnan,et al[9] .Based on individual patients NCS in post –transplant period we divide them into two cohorts Cohort 1- NCS parameters improved

Tab.10-Cohort 2- NCS parameters worsened or no change

Parameter	Cohort 1	Cohort 2	p value
No	17	3	ns
M:F	13:4	3:0	ns
Age in years	30.4	37.3	ns
Duration of CKD in months	16.3	18.6	ns
Duration of HD in months	11.4	18.5	P< .05

The only statistically significant association in cohort 2 is duration of HD.Its probable that the axonapathy may take a longer time to recover. A follow-up study at 6 ,12and24 months would give a answer.

LIMITATIONS OF OUR STUDY

Our cohort is small (30 patients).Males and females are not equally represented.NKD is not known in many patients.We have not ruled out ANCA negative vasculitis, heavy metal poisoning Amyloidosis as the cases of CKD (or) neuropathy.The follow up periods is short (3 months post transplant)The neurotoxic side effects of CNI s (Tacrolimus or Cyclosporine)on long term neurological recovery is not known.

CONCLUSIONS

1. Peripheral neuropathy in CKD is common and its prevalence increases with duration of CKD and dialysis
2. Many patients may not have overt symptoms but NCS can detect abnormalities.
3. It is a predominantly distal symmetrical sensory or sensorimotor neuropathy (sensory>motor) with lowerlimb involved more than upper limb .
4. Its predominantly axonal polyneuropathy with secondary demyelination.
5. Post renal transplantation there is improvement in conduction velocity and amplitudes earlier due to segmental remyelination.
6. In some patients recovery may take a longer time.

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