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Original Article

Is uremic neuropathy related to adequacy and duration of hemodialysis therapy? A cross-sectional analysis of neurophysiologic parameters in long term hemodialysis patients

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Abstract

Background: Uremic polyneuropathy is the most common type of peripheral nerve involvement in chronic hemodialysis patients. However, its incidence was variable and ranged from 18-83%. The aim of the present study was to evaluate the prevalence of uremic neuropathy in chronic hemodialysis patients both clinically and electrophysiologically. In addition, the effects of dialysis adequacy and duration on the extent of peripheral nerve involvement were further examined.
Patients and methods: Thirty stable chronic non diabetic hemodialysis patients (13 males, 17 females, mean age 39.17±11.52 years) were divided into three groups according to the duration of hemodialysis. Careful neurological examination as well as nerve conduction studies of both extremities were done and the results were compared to healthy control measurements. Hemodialysis adequacy was assessed through the calculation of single (spKt/V) and equilibrated Kt/V(eqKt/V) in order to examine the effect of dialysis adequacy on nerve conduction measurements.
Results: Clinical neurological examination revealed the presence of peripheral neuropathy in 57% of hemodialysis patients. There were significant reductions in the left common peroneal nerve and the right posterior tibial nerve conduction velocities as well as prolongation of the distal motor latency of the previous mentioned nerves ($P<0.05$). Sensory conduction studies revealed reduction in the conduction velocity of the left medial planter nerve besides prolongation of its distal motor latency ($P<0.05$). There were no significant correlations between all neurophysiologic measurements and either spKt/V or eqKt/V.
Similarly, no significant correlation was demonstrated between neurophysiologic measurements of the lower extremities and the duration of hemodialysis. In the upper extremities, there was a significant positive correlation between the left median nerve distal motor latency and the duration of hemodialysis ($P<0.05$).
Conclusion: Our data confirm the high prevalence of uremic neuropathy in hemodialysis patients. However, adequacy of dialysis, as indicated by urea clearance, probably doesn't play a major role in the development and progression of uremic neuropathy. Care should be exercised in interpreting the findings of nerve conduction studies of the upper extremities so as to eliminate the effect of entrapment neuropathy, particularly in long standing hemodialysis.

Key words: Hemodialysis; dialysis adequacy; nerve conduction studies; uremic neuropathy

Introduction

Nervous system dysfunction is common among uremic patients and contributes significantly to their overall morbidity and mortality [1]. Central nervous manifestations are frequent and occur early, often with subtle changes in cognitive functions, memory and disturbance in sleep [2].
Peripheral neurological manifestations appear as distal, symmetrical motor and sensory polyneuropathy affecting lower extremities more than upper extremities [3]. Usually, clinical manifestations of uremic neuropathy have insidious onset and include symmetric sensory/motor polyneuropathy [4]. The incidence of polyneuropathy in patients on hemodialysis (HD) is variable and ranged from 18-83% [5,6,7,8]. The major factors contributing to the degree of neuropathy are gender, degree and duration of renal failure [6]. In addition, autonomic dysfunction is a well-known complication of uremic neuropathy and includes dizziness, postural hypotension, heart rate variability and impotence [4].

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Pathologically, uremic polyneuropathy represents a primary axonal disease with secondary segmental demyelination. All fibers sizes, both myelinated and unmyelinated are affected though the largest and the most distal are especially vulnerable [9]. However, the pathologic findings are nonspecific for uremia and can not be distinguished from other causes of axonal degeneration [10].

The pathogenesis of uremic neuropathy is still unclear and various factors including uremic toxins were blamed to play a major role in the pathogenesis of uremic neuropathy [11]. Middle molecules were considered candidates that mostly contribute to uremic neuropathy and were correlated with depression of nerve conduction velocities in experimental animals [12]. Among the potential uremic neurotoxins implicated in uremic neuropathy is parathyroid hormone (PTH) and it was suggested that PTH elevation led to an increase in the neuronal intracellular calcium content resulting in impaired nerve conduction velocity [13]. On the contrary, several studies on hemodialysis patients had shown that PTH had no role in the etiology of uremic neuropathy [14,15].

Electrophysiological examination of motor and sensory nerve conduction velocity is the usual method to estimate the severity of uremic neuropathy [11]. Both motor, sensory and autonomic conduction velocities were reduced in chronic renal failure [16]. In addition, prolonged F wave latencies of tibial and peroneal nerves with prolonged H reflexes were the profound abnormalities detected in hemodialysis patients [17].

The study was designed to investigate the prevalence of peripheral neuropathy in a group of hemodialysis patients. In addition, we examined the potential correlation between the extent of uremic neuropathy on one hand and the duration and adequacy of dialysis therapy on the other hand.

Material and methods

Thirty chronic stable hemodialysis patients were recruited from the hemodialysis unit at the Kasr El-Aini Teaching Hospital during the period November 2001 to June 2002. They were thirteen males (43%) and seventeen females (57%) with mean age of 39.17±11.52 years and a range of 20-60 years. The etiology of end stage renal failure was angionephrosclerosis in 6 cases (20%), interstitial nephritis in 5 cases (16.66%), obstructive uropathy in 5 cases (16.66%), polycystic kidney disease in 2 cases (6.66), analgesic nephropathy in 3 cases (10%), and the cause was unknown in 9 cases (30%). The patients received thrice weekly hemodialysis sessions for 3-5 hours. Vascular access was achieved through either arterio-venous (AV) fistula in 80 % of cases (60 % left sided and 40 % right sided AV) or long term internal jugular catheter in 20 % of the cases. The blood flow ranged from 300 to 500 ml/m, the dialysate flow rate was 500 ml per minute and cello-synthetic (Hemophan 25 H) dialyzers 1.3 m^2 (AFRI Medical Co. Egypt, IDEMSA.Spain) were used. The duration of hemodialysis therapy ranged from one year to thirteen years (mean±SD 6.17±3.51). The patients were divided into three groups according to duration of hemodialysis as follows:

Group I (n=10:) Less than five years on HD (mean±SD 2.6±1.26).

Group II (n=10): More than five years and less than 10 years on HD (mean±SD 6.3±0.94).

Group III (n=10): More than 10 years on HD (mean±SD 11.5±2.41).

In addition, we included fifteen age and gender matched healthy volunteers as controls; they were six males (40%) and nine females (60%) with an age range of 22-55 years and mean of 38.6±9.23.

All the study groups gave informed consent and were subjected to thorough history taking with particular attention to neurological symptoms in the form of motor system affection (weakness, wasting and paralysis), sensory affection (pain, hypothesia, parathesia and anesthesia) and symptoms suggestive of autonomic dysfunction (orthostatic lightheadness, dizziness, sweating and impotence). Furthermore, complete neurological examination was carried out to assess the motor system (muscle tone, power and reflexes), sensory system (deep and superficial sensation) and autonomic dysfunction (postural hypotension). Routine laboratory assessment included blood urea, serum creatinine, hemoglobin percentage and serum sodium, potassium, calcium and magnesium. Table 1 showed the baseline characteristics of the study groups.

Exclusion criteria

Patients with diabetes mellitus, amyloidosis, alcoholism, hepatitis C infection, HIV infection, collagen vascular disease and chronic liver disease were excluded from this study.

Table 1. The baseline characteristics of the studied groups (mean±SD)

Parameter	*Patients*	*Controls*	*P Value*
Age (years)	39.17±11.52	38.6±9.23	>0.05
Gender (M/F)	13/17	6/9	>0.05
Duration of HD (years)	6.80±3.51		
Hemoglobin (g/dl)	8.33±1.31	12.65±2.79	<0.05*
Blood Urea (mg/dl)	169.46±40.26	29.94±5.73	<0.05*
Serum creatinine (mg/dl)	10.66±2.65	0.84±0.41	<0.05*
Serum sodium (mEq/L)	136.13±2.72	134.96±2.16	>0.05

Serum potassium (mEq/L)	5.00±0.63	3.52±0.23	<0.05*
Serum calcium (mg/dl)	7.71±1.22	9.24±1.26	<0.05*
Serum magnesium (mEq/L)	1.70±0.33	1.89±0.41	>0.05
spKt/V	1.21±0.19		
eqKt/V	1.04±0.15		

* P<0.05 is significant

Evaluation of dialysis adequacy

Dialysis dose (spKt/V) was assessed based on the Daugirdas second-generation formula [18]: spKt/V=-In (R- 0.008X T) + (4- 3.5X R) X UF/W, where In represents a function called the natural logarithm, R is defined as post serum urea nitrogen (SUN)/pre SUN, T is the session length in hours, UF is the volume of fluid removed during dialysis in liters, and W is the post dialysis body weight in Kg. Postdialysis blood urea nitrogen sample was obtained at the end of dialysis session by slowing the blood pump to 50-100 ml/minute for 10-20 seconds, after that the blood pump was stopped and a blood sample was obtained either from the arterial blood line sampling port or from the tubing attached to the arterial needle [19]. Equilibrated Kt/V (eqKt/V) was also calculated as it reflects better the true amount of therapy being delivered and can identify those with large degree of post dialysis urea rebound [20]. eqKt/V was calculated from spKt/V using Daugirdas formula [19]: eqKt/V= spKt/V-0.6X (spKt/V) / T+ 0.03

Nerve conduction studies

We used bipolar stimulating surface electrodes which were two silver discs covered with lent and soaked in saline. They were held in Perspex 2.5 cm apart and were arranged so that the cathode, which is the active electrode, was closer to the recording electrode.

a) Motor nerve conduction studies: Motor nerve conduction studies were done for the right ulnar and the left median nerves in the upper limbs and the left common peroneal and the right posterior tibial nerves in the lower limbs. The ulnar nerve was stimulated at the wrist and behind medial epicondyle of the humerus and motor evoked potentials were recorded by means of surface electrodes placed over hypothenar muscles. The median nerve was stimulated at the wrist and at the elbow and the response was recorded from the thenar muscles.
The common peroneal nerve was stimulated above the ankle and behind the head of the fibula and the motor evoked potentials were recorded from the extensor digitorum brevis muscle. Similarly, the posterior tibial nerve was stimulated at the ankle and knee and the response was recorded from abductor hallucis muscle. The motor latencies were measured at the sites of stimulation of the above mentioned nerves.
Motor nerve conduction velocity (MCV) was determined between each of the successive sites of stimulation as from elbow to wrist in the upper limbs and from knee to ankle in lower limbs. Conduction velocity was calculated as follows:

$$\text{Conduction velocity (meter per second)} = \frac{\text{Distance (in millimeters)}}{\text{Differences in latency (in milliseconds)}}$$

The difference in latency is calculated by subtracting the distal from proximal latencies to give the conduction time taken between the proximal and distal sites of stimulation. The motor evoked potentials recorded after supramaximal stimulation at proximal and distal sites were analyzed for latency in milliseconds and amplitude in microvolt.
b) Sensory nerve conduction studies: Sensory nerve conduction of the left ulnar nerve in the upper limbs and the left medial plantar nerve in the lower limbs was examined by antidromic stimulation at the wrist and behind medial malleolus respectively using ring electrode wrapped around the base of distal and proximal phalanges of the little finger and big toe respectively.
c) Sympathetic nerve conduction studies:

1. Stimulating electrodes: Bipolar stimulator surface electrodes were used. They were applied to the wrist joint of the contralateral upper limb and to the planter surface at the mid foot of the contralateral lower limb. The stimulator was usually positioned so that the cathode is directed proximally while the ground between the recording electrodes and the stimulating one. The resistance check was usually less than 5 Kohms.
2. Recording electrodes: Surface disk electrode one-cm diameter stained steel was applied with adhesive paste after thorough cleaning with alcohol. They were applied as follows; in the upper limb, the active electrode was placed over the second palmer interspace, three cm proximal to the web space, whereas the reference electrode was placed over the pulp of the middle finger. In the lower limbs, the active electrode was placed over the second interspace in the mid foot and the reference electrode was placed at the pulp of second toe.

The recording was from the left side and the stimulation to the right side at the upper or the lower limbs. The intensity of stimulation was 20 mA, with a rate of stimulation 0.1/sec with an interstimulus interval of one minute. Low filter was 0.5 Hz and high filter was 5 kHz. The latency (time between stimulus artifact, the beginning of the response) and the amplitude (the peak to peak differences) were measured.

Statistics

The results were summarized as mean±standard deviation (SD). Analysis of variance (ANOVA) was

used for testing the significance of differences in the values measured in the nerve conduction studies in the normal controls and hemodialysis patients. Correlation between different variables was examined by linear regression analysis. P values less than 0.05 were taken as statistically significant. All these analyses were performed using the SPSS/PC+ package (SPSS Inc., Chicago, IL, USA).

Results

1. Clinical neurological assessmen: 17 patients (56.66%) (6 patients in each group I & II and 5 in group III) showed evidence of peripheral neuropathy in the form of distal motor weakness that affected the lower extremities more than the upper extremities and /or distal sensory polyneuropathy with varying degrees of sensory hypothesia in glove and stock distribution and variable degrees of diminished deep sensation. In addition, five patients in group III (16.66%) had postural hypotension that was demonstrated in the interdialytic period.

2. Electrophysiological assessmen: Electrophysiological studies of patients groups were summarized in table 2.
Motor conduction studies: Compared to healthy controls, the left common peroneal (LCP) nerve and the right posterior tibial (RPT) nerve conduction velocities were significantly reduced (P<0.001). In addition, the left common peroneal (LCP) nerve and the right posterior tibial (RPT) nerve distal motor latencies were significantly prolonged in patients (P<0.05). On the other hand, the left median nerve (LM) distal motor latency was prolonged, however, the differences were not significant (P>0.05).
Sensory conduction studies: Left medial plantar (LMP) nerve conduction velocity and distal motor latency were significantly reduced and prolonged respectively compared to the control group (P<0.05 and <0.001 respectively). However, the left ulnar nerve (LU) conduction velocity and latency measurements were similar among patients compared to controls (P>0.05).
Sympathetic conduction studies: Both upper and lower limbs sympathetic nerve latency and amplitude measurements were similar among patients compared to controls (P>0.05).

Table 2. Electrophysiological studies among patients and control groups (mean±SD)

Parameter	*Patients*	*Controls*	*P value*
LCP latency (m.sec)	5.26±0.74	3.39±0.46	<0.001*
LCP amplitude (millivolts)	3.85±2.63	3.52±1.15	0.66
LCP CV. (m/sec)	43.61±8.93	56.28±3.85	<0.001*
RPT latency (m.sec)	5.77±1.38	5.10+0.65	<0.03*
RPT amplitude (millivolts)	4.12±2.60	3.69±1.26	>0.05
RPT CV. (m/sec)	42.67+6.86	59.20+5.34	<0.001*
RU latency (m.sec)	3.46±1.14	3.30±0.3	>0.05
RU amplitude (millivolts)	4.30±2.73	3.98±1.15	>0.05
RU CV. (m/sec)	56.24±9 24	59.20±4.30	>0.05
LM latency (m.sec)	4.89±0.85	3.23±0.5	>0.05
LM amplitude (millivolts)	4.56±2.82	4.23±1.2	>0.05
LM CV. (m/sec)	55.44±9.73	54.85±2.54	>0.05
LU latency (m.sec)	3.43±1.94	3.01±0.25	>0.05
LU CV. (m/sec)	40.75±14.61	43.30±3.98	>0.05
LMP latency (m.sec)	10.22±7.78	3.16±0.26	<0.01*
LMP CV. (m/sec)	26.39±11.98	43.22±3.63	<0.05*
Upper limb latency (m.sec)	1.89+1.06	1.73+0.15	>0.05
Upper limb amplitude (millivolts)	0.98+0.60	1.14+0.65	>0.05
Lower limb latency (m.sec)	2.94+0.54	2.86+0.23	>0.05
Lower limb amplitude (millivolts)	0.43+0.12	0.63+0.65	>0.05

* P<0.05

3. Hemodialysis adequacy: Group I: Single pool Kt/V ranged from 0.92 to 1.56 (mean±SD 1.22±0.19) whereas the double pool Kt/V range was from 0.74 to 1.25 (mean±SD 1.06±0.15).
Group II: Single pool Kt/V ranged from 0.81 to 1.53 (mean±SD 1.18±0.17) whereas the double pool Kt/V range was from 0.67 to 1.34 (mean±SD 0.98±0.14).
Group III: Single pool Kt/V ranged from 1.02 to 1.40 (mean+SD 1.25±0.23) whereas the double pool Kt/V range was from 0.85 to 1.24 (mean±SD 1.09±0.18).
4. Correlation between electrophysiological findings and dialysis adequacy, duration and other laboratory parameters: No significant correlation was found between electrophysiological parameters on one hand and age, hemoglobin level, blood urea, serum creatinine, sodium, potassium, magnesium and calcium levels on the other hand. Left median nerve distal motor latency showed a positive significant correlation with the duration of dialysis (r 0.29, P<0.05). There were no significant correlations between all electrophysiological measurements and both spKt/V and eqKt/V (r 0.01 to 0.09, P>0.05 all). Finally, there was no significant differences between the three main groups regarding the nerve conduction measurements.

Discussion

The present study showed that 57% of the study patients had evidence of clinical peripheral sensory or motor polyneuropathy. In comparison to the control group, motor nerve studies have showed decrease in the conduction velocity of the left common peroneal nerve and the right posterior tibial nerve as well as prolongation of the distal motor latency of the previous mentioned nerves ($P<0.05$). On the other hand, sensory conduction studies revealed reduction in the conduction velocity of the left medial planter nerve besides prolongation of its distal motor latency, which reflects the most distal peripheral nerve function, compared to controls ($P<0.05$). This profound neuropathy was demonstrated earlier by previous studies that reported a prevalence of about 73% of uremic neuropathy in hemodialysis patients as detected by nerve conduction studies [21]. These results also highlight the basic pathological defect in uremic neuropathy that is multiple neuropathy due to axonal degeneration of the sensory and motor nerves starting from the lower extremities with secondary demyelination that produce reduction in the conduction velocity as well as prolongation of distal latency in the affected nerves [22].

Hemodialysis patients in the present study were divided into three groups according to the duration of hemodialysis and the measured values of nerve conduction studies were compared among the different groups. No significant differences were found between the study groups, however, there was a sporadic significant correlation between the left median nerve distal motor latency and the duration of hemodialysis ($P<0.05$). This would be explained in part by the reported increased incidence of carpal tunnel syndrome in the hemodialysis population with prolongation of the hemodialysis duration [17].

In fact, the effects of duration of hemodialysis on nerve conduction measurements have been conflicting. Many previous reports have consistently reported chronological reductions in nerve conduction velocities during hemodialysis [23,24]. However, a recent study had shown that the severity of uremic neuropathy remained unchanged during hemodialysis [17].

Adequacy of dialysis was measured in the present study using both single and double pool Kt/V. However, equilibrated Kt/V measurement reflects better the adequacy of dialysis as it reflects the degree of urea rebound [20]. The results revealed that mean spKt/V was 1.2 ± 0.19 and eqKt/V was 1.04 ± 0.15 which lies within the recommended range of the NKF-DOQI, 2000 [25]. In addition, there were no significant correlations between all neurophysiologic measurements and either spKt/V or eqKt/V. This may indicate that solutes with small molecular weight have a minor role in the development of uremic neuropathy. So far, two studies have focused on the effect of dialysis adequacy on the extent of uremic neuropathy. Motor nerve conduction velocity was reported to decrease much more with prolongation of hemodialysis in those with low Kt/V in one study [26]. In contrast, Jackic and colleagues failed to demonstrate any correlation between neurophysiologic parameters and dialysis dose as detected by spKt/V [11]. These findings further highlight the contribution of middle molecular weight substances (molecular mass, 300 to 1500 Dalton) to the pathogenesis of uremic neuropathy. Indeed, several studies have confirmed the neurotoxicity of middle molecular weight substances in hemodialysis [27,28]. Uremic neuropathy was more severe in patients dialyzed with low flux cuprophane (CUP) membrane compared to those dialyzed with high flux polyacrylonitrile (PAN) membranes [27]. In addition, continuous ambulatory peritoneal dialysis (CAPD) patients had less severe neuropathy as compared to hemodialysis, that could be explained in part by more effective removal of middle and larger molecules in CAPD [28]. Of Interest, Djukanovic and coworkers had shown that reduction of plasma levels of middle molecular weight substances (MMS), using AN 69 membrane, was associated with significant improvement of neuropathy in a group of hemodialysis patients [29]. Similarly, hemodiafiltration was associated with improvement in the extent of uremic neuropathy as it provides more effective removal of middle molecular weight substances than HD [30].

Finally, the results of the present study showed that 16.66% of long standing hemodialysis patients (having more than 10 years on HD) had orthostatic hypotension. Yet, the nerve conduction studies revealed normal sympathetic conduction measurements in hemodialysis patients. In fact, not all studies have reported evidence of sympathetic nervous system dysfunction in hemodialysis patients. Some studies reported abnormal sympathetic nervous system function in chronic renal failure patients [31,32], though others reported normal function [33,34]. However, we have not examined closely the integrity of the sympathetic nervous system through the assessment of the blood pressure responses to pressor stimuli including hand grip and cutaneous cold tests since that was beyond the scope of the present work. Certainly, evaluation of the sympathetic activity directly by microneurographic techniques would permit more accurate assessment of sympathetic activity in hemodialysis patients [35].

In summary, our data confirm the high prevalence of uremic neuropathy as well as electrophysiological abnormalities in hemodialysis. However, adequacy of dialysis as indicated by urea clearance seems not to play a major role in the development and progression of uremic neuropathy. Care should be exercised in interpreting the findings of nerve conduction studies of the upper extremities so as to eliminate the effect of entrapment neuropathy, particularly in long standing hemodialysis.

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