Original Research Article

Study on prevalence of peripheral neuropathy among patients on hemodialysis

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Abstract

Background: The incidence and prevalence of Chronic Kidney Disease is increasing slowly. Peripheral Neuropathy among CKD patients is the most common neurological complication of uremia, but still it is an under estimated problem adversely affecting the patient's quality of life. It is more often a silent burden for the patient, progressively affecting his/her quality of life. Hence, this study aimed at analyzing and elaborating the diverse manifestations of CKD and establish the prevalence of peripheral neuropathy among patients with CKD undergoing hemodialysis in our Hospital.

Materials and methods: This was a cross sectional study done on patients with CKD undergoing hemodialysis at Government Vellore Medical college and Hospital for a duration of 6 months from July 2017 to December 2017. After obtaining informed consent, the participants satisfying the inclusion criteria were asked detailed history and clinical examination was performed according to the well-designed proforma cited below. The presence of neuropathy was assessed using Michigan Neuropathy Screening Instrument (MNSI) Scores.

Results: The mean age of the study subjects was 47.87 years. Most of the patients belonged to the age group 40-70 years. Out of 60 cases, there were 35 (58.0%) males and 25 (42.0%) females. The Male to Female sex ratio was 1.38:1. The prevalence of clinical Uremic distal symmetrical sensory-motor peripheral neuropathy assessed by MNSI in the CKD on HD population was 71.66%. The smallest MNSI score obtained in the study population was 2 and the largest score was 7.

Conclusion: Uremic neuropathy is the most common neurological complication in patients with uraemia. MNSI physical assessment could be used as a simple bed side examination to determine the presence or absence of uremic peripheral neuropathy.

Key words

Chronic kidney disease, Hemodialysis, Uremia, Peripheral neuropathy.

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem. There are several etiologies for CKD. It can occur due to either a primary kidney disease or as a complication of a multi-systemic disorder [1]. Much emphasis has been placed on the increased cardiovascular risk and electrolyte abnormalities that accompany chronic kidney disease. The dreaded neurological complication is usually the uremic encephalopathy or a vascular event that accompanies hypertension.

DM is the most common cause in developed nations, whereas inflammatory kidney disease, namely glomerulonephritis and interstitial nephritis remains the most common causes in developing countries [2]. DM along with hypertension - the second most common cause – and glomerulonephritis accounts for about 75% of all adult cases. In young adults a common etiology of CKD is genetic kidney disease [3].

The estimated prevalence of CKD in India is around 0.78% -0.8% [4]. The rate of which is increasing slowly. A rough age adjusted incidence of CKD stage V or End Stage Renal Disease (ESRD) is around 151 and 232 per million population respectively [5].

Though the occurrence of Peripheral Neuropathy in patients with Renal Failure has been known for over a Century, it was not fully recognized till the middle of 20th century. Before the implementation of chronic dialysis for patients with ESRD, the patients usually did not survive long enough to develop peripheral neuropathy that can be clinically diagnosed. Up to Sixty five percent of the patients develop Peripheral neuropathy, before or in a short span of time after putting them on dialysis.

The exact metabolic abnormality causing Uremic neuropathy has not been made out yet. A number of observations have been made with regards to potential urotoxins that can cause peripheral neuropathy. Some of the few identified toxins are guanidine compounds, parathyroid hormone, middle molecules, myoinositol and so on. They are implicated but are not established causes of peripheral neuropathy [6].

In the initial days of renal replacement therapy the concept of 'middle molecules' as the likely candidate for causing uremic neuropathy was put into focus. Though the proof was mainly observational, the concept stayed for a quite a long time [7]. The observation that dialysis considerably improves the uremic symptoms only augmented the speculation that schribner postulated that the compounds causing neuropathy should be the middle molecules with molecular weight ranging between 500 to 2000 daltons. These compounds are however larger than Urea and Creatinine and so are cleared by dialysis at a much lower rate than urea and creatinine which are the usual measure of biochemical control of uremia.

Uremic neuropathy is primarily an axonopathy caused due to decreased energy supply by inhibiting enzymes required to maintain energy production as postulated by Fraser and Arieff [8]. Pathological research on uremic neuropathy is far and few when compared to the clinical research. Most of these were sural nerve biopsy studies; Metabolic derangement in Schwann cells is thought to be the culprit. According to Asbury et al, postulated that the neuropathy is similar to axonal degeneration of other causes. Since it's an axonopathy, the nerve fibres which are long are affected compared to shorter fibres because the metabolic needs of the peri karyon with a longer fibre is not adequately met in comparison with the shorter fibres. This results in dying back neuropathy. Electron microscopic changes reveals splitting of the myelin lamellae, and detachment of lamella from subjacent axolemma

with smaller mitochondrial abnormalities. Neurofilamental or neurotubular derangements are not usually seen. These changes are found in any number of neuropathy and are not exclusive to Uremic neuropathy.

Uremic neuropathy has a vast spectrum of neurological manifestations but the most common manifestation of uremic neuropathy is Distal symmetrical, mixed motor and sensory polyneuropathy. Since it is predominantly an axonopathy the longer axons are affected first manifesting as predominantly involving lower limb more than the upper limb. The degree of peripheral neuropathy depends on a lot of factors including the duration of renal insufficiency, eGFR, duration of dialysis and so on. Uremic peripheral neuropathy is an insidious onset slowly progressive distal neuropathy predominantly presenting with complaints of tingling, prickling, pins and needles and restless leg syndrome.

- Paresthesia is one of the common and initial clinical presentations.
- Hyperalgesia is an important symptom.
- Paresis and atrophy of the muscles of lower extremities closely follow the sensory symptoms. The dying back axons in due time involve proximal group of muscles and starts to involve the upper limb.
- Muscle cramps and restless legs syndrome which is characterized by bizzare crawling sensations, quickly resolving with change in limb posture were reported to involve 67% of patients with uremic neuropathy patients, although it is also found in patients without uremic neuropathy.

Uremic myopathy is also an important cause of fatiguability in CKD patients frequently causing myopathic weakness and exercise limitation. It is characterized by muscular atrophy in the final stages [9].

Renal replacement therapy has resulted in halting of the symptoms of uremic peripheral neuropathy or even reversal but sometimes there might not be any improvement as well. The rate of reversibility depends on various parameters such as duration of symptoms, type of renal replacement therapy, frequency of dialysis and so on. Renal transplant provides the best possible results out of all the current therapies available aimed at alleviating uremic peripheral neuropathy. Electrophysiological study is the Gold standard method in assessing peripheral nerve function. Preswick in 1964 [10] has demonstrated that decrease in conduction velocity is a common finding in uremic cases with no external manifestations of neuropathy.

Many viable urotoxins have been discovered which has decreased the motor nerve conduction velocity (MNCV) in experimental animals [11]. The MNCV has been a principle test for determining neuron function. This study is primarily aimed at estimating the prevalence of peripheral neuropathy in patients with CKD in a tertiary care hospital including those on renal replacement therapy.

Objective

- To study the prevalence of peripheral neuropathy in patients with chronic kidney disease undergoing hemodialysis at GVMCH.

Materials and methods

Study design

Cross sectional study

Study population

This study was carried out in chronic kidney disease patients attending hemodialysis unit and patients admitted as in-patients in our medical wards in the department of General medicine, Government Vellore Medical College and Hospital.

Study period

July 2017 to December 2017

Sampling method

Convenient sampling technique was used.

Inclusion criteria

- All patients irrespective of age and sex with the chronic kidney disease.
- eGFR <60ml/min/1.73^2 determined by MDRD formula (186.3 x (Creatitine in mg/dl)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female)
- Ultrasound abdomen evidence of CKD like reduced renal cortical thickness, increased renal cortical echogenicity or reduced renal length <9cm

All patients included in the study had chronic kidney disease.

Defined as abnormalities of kidney structure or function for 3 months or longer with implications for health (**KDIGO 2012 CKD nomenclature**). Patients at the time of evaluation were on Hemodialysis 4 hour duration and 3cycles per week. None of the patient were on peritoneal dialysis.

Exclusion criteria

- Patients denying Consent
- Patients who had renal transplant
- Patient with other known cause of peripheral neuropathy such as Hypothyroidism, Alcohol, Diabetes Mellitus, Tuberculosis, Hansen's disease, Patients on drugs having peripheral neuropathy as established toxicity, malignancy and vitamin B12 deficiencies.

Methodology

Patients after satisfying the inclusion criteria were included in the study. A total of 60 patients were included in the study, they were asked detailed history regarding the duration of uremic symptoms, whether the patient is already on any renal replacement therapy and the duration of his hemodialysis. The patient was asked to answer questions from Michigan Neuropathy Screening Instrument MNSI questionnaire. Then physical assessment according to MNSI physical assessment chart would be carried out and points filled.

Statistical analysis

Statistical analysis was done using the SPSS v16 software. Quantitative data were expressed in mean, minimum, maximum and standard deviation. The qualitative data was expressed by Chi-Square test. The difference was considered statistically significant if p value was ≤ 0.05.

Operational guidelines

Peripheral neuropathy was considered to be present if

1. ≥7 MNSI questionnaire
2. ≥3 MNSI physical assessment score

Results

During the period of study, 60 patients diagnosed to have chronic kidney disease on HD were included in the study after satisfying the inclusion criteria and the following observations were made.

Age

The mean age of the study group was 47.87 years, with a minimum of 16 years and a maximum of 84 years with a mean of 47.87 years ±14.76 years. Most of the patients belonged to the age group of 40-70 years of age (**Table – 1**).

Sex

Out of 60 cases, there were 35(58.0%) males and 25 (42.0%) females. The Male to Female sex ratio was 1.38:1.

Age and sex distribution

Of the total number of patients, there were 8 patients who belonged to the age group of <30 years, of which there were 3 males and 5 females. A total of 24 patients belonged to the age group of 21 – 50 years of age of which there were 14 males and 10 females. There were 17 patients who belonged to the age group of 50 - 60 years of age of which there were 10 males and 7 females. 11 patients belonged to the age group of >60 years of age of which 8 patients were male and 3 patients were female (**Table – 2**).

Table - 1: Age distribution.

	N	Minimum age in years	Maximum age in years	Mean
Age	60	16	84	47.87

Table - 2: Age and sex distribution.

Age (in years)	Male	Female	Total	Percentage (%)
<30	3	5	8	13.0%
31-40	7	5	12	21.0%
41-50	7	5	12	21.0%
51-60	10	7	17	28.0%
61-70	4	3	7	11.0%
>70	4	-	4	6.0%

Table - 3: CKD on HD & UPN.

CKD on HD	UPN		Total
	Present	Absent	
Male	26(73.80%)	9(26.20%)	35
Female	17(68%)	8(32%)	25
Total	43	17	60

Table - 4: UPN & HD duration.

HD duration	UPN		Total
	Present	Absent	
1-12 months	28(65.11%)	15	43
13-24 months	15(88.23%)	2	17
Total	43	17	60

Table - 5: The most frequent signs observed.

S. No	Abnormal MNSI signs	Percentage
1	Appearance of Feet	0%
2	Ulcerations	4.12%
3	Absent ankle reflex	40.20%
4	Absent Vibration perception	21.64%
5	Abnormal Monofilament test	34.02%

Prevalence of peripheral neuropathy

In the HD group out of 60 patients, 43 patients (71.6%) were diagnosed as having clinical peripheral neuropathy and 17 patients (28.33%) had not satisfied the diagnosis of clinical peripheral neuropathy (**Table – 3**).

Out of the 43 patients, 26 patients who had peripheral neuropathy were males and 17 patients were females, whereas, out of 17 patients who did not have peripheral neuropathy 9 were males and 8 were females.

Duration of HD and UPN

The Minimum duration of HD was 2 months and the maximum duration was 24 months with a mean of 6.50 months±6.829. Out of 43 patients who had HD duration between 1-12 months the peripheral neuropathy was present in 28 patients and in patients having HD duration between 12

to 24 months the peripheral neuropathy was present in 15 patients (**Table – 4**).

The presence of peripheral neuropathy and Duration of HD are not statistically significant. χ^2=0.41 with 1 degree of freedom and p value=0.840 (p value >0.05).

MNSI and uremic peripheral neuropathy

The smallest MNSI score obtained in the study population was 2 and the largest score was 7 with a mean score of 2.580 with a standard deviation of 2.069.

In the study population, 1 patient (2%) have scored MNSI scores between 1-2.5 out of 10 and 35 patients (58%) had scored between 3-5.5 out of 10.

Patients who have scored 6-10 points are 20 patients. Rest of the patients has not scored any points in MNSI.

Absent ankle reflex was the most common finding in the study. The second most common finding in the study was abnormal monofilament test which was followed by absent vibration perception (**Table – 5**).

Discussion

Uremic neuropathy is often the commonest complication of the uremic syndrome and is defined as a predominantly distal sensori-motor polyneuropathy that predominantly affects the distal segments more so in the lower limbs than in the upper limbs which may occasionally present as a mononeuropathy due to compression, trauma or ischemia [12]. The condition is often silent burden among patients with CKD affecting the quality of life considerably. The prevalence of peripheral neuropathy due to uremia may range from 70-100% in patients with End stage renal disease [13].

Sixty adult patients with CKD attending the HD ward for thrice weekly dialysis or patients admitted in the medical wards of our institution were included in our study. The mean age of the study population was 47.87 years with a male to female ratio of 1.38:1.

Age and gender

In a study by Jedras M, et al. [14], conducted in 51 patients on chronic hemodialysis, Males were found to be having more sensori-motor neuropathy when compared to women, whereas women were found to have more prevalent autonomic neuropathy when compared to men. In our study males were significantly more affected by peripheral neuropathy when compared to females. With respect to age in our study it was found that patients aged ≥60 years were predominantly affected by uremic neuropathy which was statistically very significant (p value <0.01).

Michigan neuropathy screening instrument physical assessment (MNSI)

Mambelli E, et al. [15], conducted a study on 225 dialysis patients to determine the prevalence of uremic neuropathy, all causes inducing secondary neuropathy were excluded from the study. MNSI scores and Electroneurography of the lower limb was conducted to compare the sensory nerve conduction velocities and sensory nerve action potential results with MNSI results. 37 patients (16.4%) were identified to have uremic neuropathy. There was a significant correlation between MNSI scores (>or equal to 3) between MNSI physical assessment and SCV (r^2=0.1959; p <0.034) as well as SNAP (r^2=0.3454; p=0.027) both measured by ENG. Nine patients from his study has scored less than 3 in MNSI in spite of neuropathic assessment. He concluded the study by saying that MNSI could represent a valid and simple clinical-instrumental screening test for the early diagnosis of UN in view of an early therapeutic approach.

In our study the smallest MNSI score obtained in the study population was 2 and the largest score was 7 with a mean score of 2.580 with a standard deviation of 2.069. In the study population, 1 patient (2%) have scored MNSI scores between

1-2.5 out of 10 and 35 patients (58%) had scored between 3-5.5 out of 10.

Signs

Al-Hayk and Bertorini stated that earliest finding of uremic neuropathy are loss of Achilles reflex and increased vibrating sensation threshold. Several other studies concluded that paired vibratory sense in the lower limbs and loss of deep tendon reflexes, first ankle jerks and then knee jerks, are the usual first signs of peripheral neuropathy. In comparison to sensory, the distal motor sensory neuropathy was the common type with chronic kidney disease.

In our study, the most frequent sign observed was absent ankle reflex (40.20%) which is consistent with the predominant large fibre involvement in uremic neuropathy, the next common sign was abnormal monofilament test (34.02%) and absent vibration perception (21.64%).

Prevalence of uremic peripheral neuropathy in CKD patients

The prevalence of uremic neuropathy is 60%-100% of patients on dialysis [13]. Neuropathy generally only develops at glomerular filtration rates of less than 12 ml/min/1.73^{2}BSA.

In stage V CKD (on HD) patients the prevalence of clinical uremic peripheral neuropathy was 71.6% which was clinically and statistically significant.

The course of neuropathy is variable in patients undergoing dialysis. Routine Hemodialysis has found not to improve neuropathy in patients with CKD despite decrease in urea and creatinine levels, this was emphasized by many workers [16]. Lengthening the time on dialysis/week (more "square meter hours" i.e., membrane area multiplied by dialysis time) prevents neuropathy. Despite elevated urea and creatinine levels, peritoneal dialysis improves peripheral neuropathy better than hemodialysis.

These findings correlate with the observations of Asbury, that, in the past decades, the occurrence of clinically evident neuropathy in patients on chronic dialysis program (both hemodialysis and peritoneal dialysis) has become rare, as a result of earlier institution of treatment, frequent dialysis scheduling and improvement in dialysis techniques.

Limitations

The main limitation of the present study relates primarily to the size of the sample. This limitation arises from the fact that only few patients under chronic hemodialysis maintenance treatment in the dialysis unit at GVMCH fulfilled the study criteria. A study carried out in a longer period of time, would allow the inclusion of more people and so, it would perhaps make statistically significant some trends shown in this study.

Conclusion

The present study emphasizes the high prevalence of peripheral neuropathy in a group of patients with end-stage kidney disease under hemodialysis maintenance treatment. Despite the short period of time the study was conducted and, consequently, small sample's size, the obtained results allow us to highlight the huge importance of having neurologists and nephrologists as well as other specialists working all together to better diagnose and manage neurological complications of end-stage kidney disease in these patients. Its importance is increasing because CKD has become worldwide a public health issue. Since some patients with CKD have subclinical peripheral neuropathy and neurological complications impair their quality of life, early diagnosis of this condition is essential. The gold standard exam for diagnosis confirmation is nerve conduction studies. Thus, before undergoing dialysis, it would be recommended to submit all patients with CKD to nerve conduction studies.

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