

Severity of Chronic Kidney Disease Associated Pruritus Clinically Related to Symptomatic Pheripheral Neuropathy in Patients of End Stage Renal Disease On Maintenance Hemodialysis: Our Experience

Puneeta Gupta*, Rajesh Gupta

Abstract

Uremic pruritus is known to affect about 20%-50% of patients with end-stage renal disease and has been associated with poor quality of life, poor sleep, depression, and is an independent risk factor for increased mortality. The aim of present study was to study the clinical correlation between the symptoms of pheripheral neuropathy and severity of pruritus. The study included 60 patients coming to the hemodialysis unit for a period of one and half year . Results; The neuropathy was diagnosed in 18 (69%) out of 26 patients in pruritus group and 10 (29%) out of 34 patients in the non-pruritus group. The results of our study confirm the close clinical co-relationship between the severity of pruritus to that of symptomatic peripheral neuropathy.

Key Words

Chronic Kidney Disease-Associated Pruritus" (CKD-aP), Peripheral Neuropathy , Chronic Kidney Disease (CKD), Uremia, End-Stage Renal Disease(ESRD), Itching

Introduction

The word "uremic pruritus" has been used for symptoms of itching because it is a common in patients with advanced renal disease. affecting about 20%-90% of patients.(1-3) Peripheral neuropathy induced by uremia, is another very common and disabling symptom in patients of chronic kidney disease with reported incidence ranging from 15 to 85 % in various studies.(4)The etiologies of both these conditions are not clear and although for long it has been believed to be caused by the accumulations of uremic toxins, this hypothesis is not sufficient to explain the symptoms as majority of patients of ESRD continue to be symptomatic , despite attaining current targets of dialysis adequacy . Moreover , some of the patients will complain of these symptoms only after they are started on renal replacement therapy (RRT) .Thus it follows that both pruritus and peripheral neuropathy remain inadequately treated in patients of ESRD resulting in significant impairment in quality of life. Apart from physical discomfort pruritus affects social and psychological aspects of the life significantly. ESRD patients with CKD-aP have higher mortality rates than patients without pruritus which have

been reported to be as higher as 13% in DOPPS I(Dialysis Outcomes And Practice Patterns Study) , 21% in DOPPS II, and 37% in another study ;as compared to patients without pruritus (1-4). The neurophysiology of pain and pruritus appears to be similar and it has been suggested that the pathways carrying both neuropathic pain and pruritus are similar but not the same and this analogy allows a correlation between the two symptoms (5,6).In fact the visual analogue scale (7), (VAS) which is commonly used to measure CKD-aP severity, was first developed to measure pain including neuropathic pain .(7,8)

Thus, the present study was done to evaluate the clinical correlation between the symptoms of peripheral neuropathy and severity of pruritus in patients of ESRD on maintenance hemodialysis .

Material and Methods

The 60 patients coming to the hemodialysis unit of Acharya Shri Chander College of Medical Sciences were selected for the study which lasted for 18 months ,The patients who were on maintenance hemodialysis for at least 3 months , were over 18 years of age and who

From the PG Depart of Medicine, *ASCOMS & Government Medical College, Jammu J&K India

Correspondence to : Dr. Puneeta Gupta, Associate Professor, Depart. of Medicine, ASCOMS & Hospital, Sidhra, Jammu -J&K- India

Fig.1 Age wise distribution of CKD patients

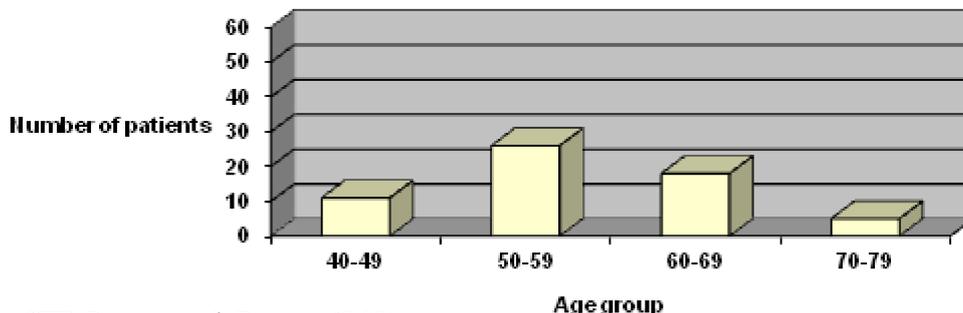
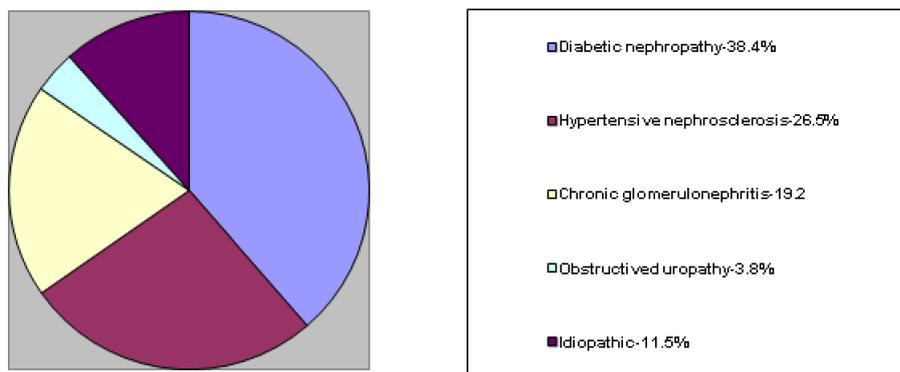


Fig.2 Etiology in CKD Patients with Pruritis 43.3%



agreed to participate in the research by signing an informed consent, were included in the study .

Case group patients were examined to rule out other causes of pruritus and patients with active infection, recent hospitalization within three months, psychotic illnesses or other communication problems, primary skin disorders, cholestatic liver disease or acute hepatitis, or active malignancy were excluded from this study. The demographic and clinical characteristics, including gender, age, presence of hypertension or diabetes, underlying renal disease, concurrent medications, as well as the regimens and vintage of hemodialysis, of the participants were recorded. Venous blood was sampled in the morning, after an overnight fast exceeding 8 hours before the patient's mid-week dialysis. All laboratory tests were performed by the hospital's central laboratory.

The severity of pruritus was assessed subjectively and scored as mild for episodic and localized pruritus without disturbance in usual work and sleep, moderate for Generalized and continuous pruritus without sleep disturbance, and severe for generalized and continuous pruritus spectrum interfering with all activities of daily living including sleep. The patients with end-stage renal failure underwent basic neurological examination for the diagnosis of peripheral neuropathy which was based on the presence of symptoms of paresthesia, restless leg syndrome and on clinical examination presence of decreased sensations of vibration, position, light touch,

pain, decreased deep tendon reflexes or muscular force. . All patients who were having neuropathy on clinical examination also underwent neurophysiological procedures, as Electroneurography (ENG), consisting of Nerve Conduction Sensory Velocities Study (NCSVs) and Nerve Conduction Motor Velocities Study (NCMV), in the upper and lower limbs, included CMAPs (Compound Motor Action Potentials) and SAPs (Sensory Action Potentials), with study of latency and amplitude, of Median nerve, Peroneal nerve, Sural nerve bilaterally.

Result

The 60 patients coming for maintenance hemodialysis for at least 6 months were included in the study which included 40 males and 20 female patients

The 26 (43.3%) patients out of the sixty enrolled in study, were diagnosed with chronic kidney disease associated pruritus ,18(69.2%) of the patients being male and females comprising remaining 8 patients (30.76%) . The causes of CKD identified in these patients included diabetic nephropathy in 10 ,hypertensive nephrosclerosis in 7, chronic glomerulonephritis (CGN) in 5 ,obstructive uropathy in 01(3.8%) , and cause couldn't be ascertained in the rest 3 patients .(the p value is 0.83)

In 34 patients without pruritus ,cause of CKD was identified as diabetic nephropathy in14, hypertensive nephrosclerosis in 6, chronic glomerulonephritis (CGN) in 5,obstructive uropathy in 04 , autosomal polycystic kidney disease in 2 and cause couldn't be ascertained in

Fig.3 Etiology in CKD Patients without Pruritis 56.7%

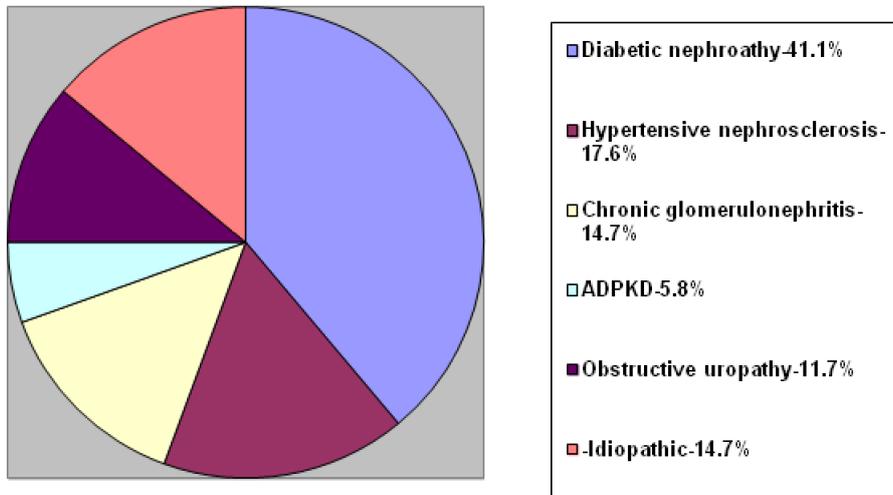


Fig.4 Percentage of Pruritis in Patients with Neuropathy

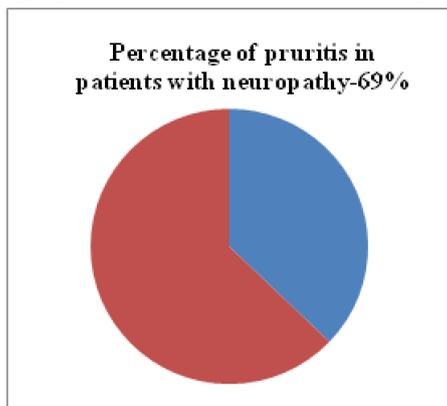
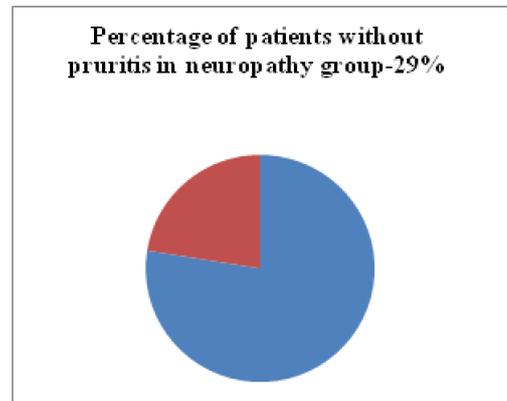


Fig.5 % of Pruritis in Patients without Neuropathy



the rest 5 patients . .When asked about the history of pruritus ,16 (61.53%) patients had onset of symptoms prior to the initiation of dialysis ,the remaining 10(38.46%) patients reported that their symptoms started after the initiation of the hemodialysis .Regarding distribution of itching ,15 (57.69%) patients had involvement of large, non-dermatomal areas with bilateral symmetry, where as in 10 (38.46%) patients, pruritus was localized ,back being the most common site .The examination to find out associated findings revealed that xerosis or excessive dryness of skin was the most common finding , reported by 14 (53.84%)patients followed by minor ulcerations in 8(30.76%) patients and papules in 5(19.23%) patients. Intensity of the pruritus was mild in nature in 10(38.46%) patients, moderate in 6 (23.07%) and 8(30.76%) patients reported severe itching

The neuropathy was diagnosed in 18 (69%) out of 26 patients in pruritus group and 10 (29%) out of 34 patients in the non-pruritus group .The meticulous neurological examination in symptomatic patients revealed a mixed sensory motor polyneuropathy, which was also confirmed

by the nerve conduction studies . The ENG results of our examined patients were as follows. A reduction in NCMV (Nerve Conduction Motor Velocity) of the peroneus nerve bilaterally in all patients, mostly marked in 8 patients, who had reported a greater intensity of pruritus. NCSV reduction (Nerve Conduction Sensitive Velocity) was also observed in all patients, as well as SAPs (Sensitive Action Potentials) was reduced in 7 patients, who revealed an increase in distal latency. Conversely, SAPs were absent in the same patients who reported a greater intensity of pruritus. These results confirmed the clinical diagnosis of bilateral sensory- motor neuropathy of the lower limbs, while the examination of the upper limbs showed normal values, upon exploration of the median nerve.

Discussion

The ueremic pruritus or more aptly the "chronic kidney disease (CKD)-associated pruritus as pruritus is usually not found in patients with acute kidney injury.(1,2)) The diagnosis of CKD-aP , which affect

about 20%-90% of patients based on variable diagnostic criteria, may be challenging because many patients with end-stage renal disease (ESRD) are suffering from other diseases, which may provoke itching either by itself or by medication given to treat these entities.(3) In the present study, the symptomatic neuropathy was more common in patients with pruritus as compared to the group without pruritus and difference was statistically significant (p value 0.002). 10 patients complained about severe symptoms in the pruritus group whereas patients reported disabling neuropathic symptoms in non-pruritic group. These findings were not confounded by the presence of diabetics in the study group, as pruritus was not significantly different between diabetics and non-diabetics patients in our study.

The wide range of prevalence rates of pruritus and neuropathy is likely related to varying characteristics of studied populations, the era when studies were performed, and the diagnostic instruments and criteria used. The mechanism of uremic neuropathy remains unclear. It is a distal, symmetrical, mixed sensorimotor neuropathy that is characterized by demyelination and axonal degeneration. Polyneuropathy generally develops only in patients with significantly reduced glomerular filtration rate (GFR) and is an indication to initiate dialysis, but importantly patients already being adequately dialyzed also develop polyneuropathy. Factors that have been suggested to contribute include deficiencies of thiamine, zinc, and biotin and decreased transketolase activity. Increases in phenols, myoinositol, beta2-microglobulin and other middle molecular weight substances which normally get accumulated in ESRD along with hyperparathyroidism have also been suggested to contribute(9,10). The pathogenesis of CKD-aP also remains incompletely understood leading to many hypothesis, like immune mediated hypothesis which suggests the role of dysregulated systemic inflammation (11) marked by high white blood cell count, low albumin, c-reactive protein, interleukin-6 and interleukin-2 level(11); over-stimulation of endogenous opioid receptors (12,13), similar to its possible role in the pathogenesis of cholestatic pruritus; an imbalance of mu and kappa-opioid receptor activity with mu-receptor over-activation and kappa receptor (14) blockade resulting in increasing itching and the increased levels of histamine, eosinophils, mast cells, and tryptase postulated to be responsible for itching by many (15,16). The two hypothesis which have received maximum attention are that of secondary hyperparathyroidism and associated derangements of calcium and phosphorus which was suggested nearly 50 years ago and causative role of uremia related toxins (17,18). Majority of the studies conducted in last 50 years, however, have

not found a consistent or statistically significant association between serum calcium and phosphorus levels, Ca/P ratio, PTHi values and size of the dialyzer with pruritus.(19)

Thus it follows that inciting factors present in the uremic milieu that trigger CKD-aP are yet unknown, and the perception and perhaps perpetuation of itch may have a prominent central nervous system component. (20,21) as suggested by abnormal nerve conduction studies seen in patients on dialysis, and the co-occurrence of CKD-aP with paraesthesia and restless leg syndrome. However, pruritus does not occur in a stocking-glove pattern characteristic of peripheral neuropathy (22-24). Conduction disorder in sensory-motor pathways is characterized by paresthesia, pricking of the feet, and uneasy foot syndrome. Pruritus may also be secondary to a reduction in the perception threshold. Nerve root damage may lead to an increased sensitivity to itching. The neurophysiology of pain and pruritus appears to be similar and it can be concluded that the pathways carrying both neuropathic pain and pruritus are similar but not the same and this analogy allows a correlation between the two symptoms. Both are conveyed by a subset of specialized C-fibers in the dorsal horns of two separate systems and transmitted to the thalamus and the somato-sensory cortex via the lateral spino-thalamic tract. It is known that painful scratching reduces itching and this can be explained because of the interaction of the pain and itching pathways. It is suggested that uremic pruritus could be due to a diminished threshold of perception, regardless of the specific causative factor. This can be the result of the peripheral nerve fiber damage due to uremic neuropathy associated with a central sensitization to itch, which may be chronically sustained by the uremic toxins. Therefore it may be assumed that one or both of neuropathic and neurogenic mechanisms may be responsible for the itch associated with chronic kidney disease. Pruritus is a sensorial symptom similar to pain perception. Pruritus neuronal pathways are constituted by myelinated C sensitive nervous fibers that receive information from skin receptors and transmit to the spinal cord, reaching the thalamic region. These fibers are placed between the epidermis and dermis layers, where they interact with keratinocytes and mast cells which release chemical mediators, such as histamine, P substance, cytokines, proteases and others. A neurobiological signal seems to then arrive to the cortical brain structures, where it is processed as pruritus. Another hypothesis considers the possibility that in uremic disease, there may be the presence of an abnormal distribution of the cutaneous innervation, suggesting that uremic patients can develop

specific dermal alterations, like different innervation pathways, which could be responsible for an elevated pruritus symptomatology, signs of hypersensitivity and reduced perception threshold, that could explain, for example, the use of gabapentin, an effective treatment of neuropathic pain, also in uremic pruritus with some success. Furthermore, some groups investigated the possible influence of the autonomic nervous system on the emergence and persistence of pruritus, by using special tests, such as sympathetic skin response (SSR) and RR Interval Variation, in basal and profound breath conditions (RRIV), but concluded that pruritus is related to somatic neuropathy more than to autonomic dysfunction (5)

Finally the reduction in the number of cutaneous nerve terminals has been demonstrated by some investigators suggesting that skin innervations can be a possible consequence of neuropathy, thus indicating that the progression of pruritus is linked to the severity of neuropathy and that the more intense the pruritus in these patients, the more severe is their neuropathy (22-24), suggesting that skin innervations can be a possible consequence of neuropathy, thus indicating that the progression of pruritus is linked to the severity of neuropathy and that the more intense the pruritus in these patients, the more severe is their neuropathy (22-24)

Conclusion

The results of our study confirm the close clinical relationship between the symptoms of pruritus and neuropathy. Both the symptoms are quite common and distressing in patients of ESRD and remains inadequately managed which justifies further research on nerve function and neurotransmitters and the introduction of new drugs targeting both neuropathy and pruritus in these patients

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