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Nephrology

THE SPECTRUM OF DERMATOLOGICAL MANIFESTATIONS IN CHRONIC KIDNEY DISEASE PATIENTS OF UDDANAM NEPHROPATHY

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ABSTRACT

Background – An increased prevalence of chronic kidney disease has been observed in several geographical areas across the world including Uddanam region in India. Many of the cutaneous disorders experienced by patients of chronic kidney disease are related to the underlying pathologic process that induced the renal disease.

Aims- This study was done in a tertiary care center to identify common dermatological manifestation in chronic kidney disease patients of Uddanam region after excluding other possible etiologies of renal dysfunction and to compare it with patients of renal dysfunction with known etiologies.

Methods- The study was an observational study of 1 yr duration. All the chronic kidney disease patients attending nephrology outpatient department (OPD) and patients undergoing regular dialysis in the hospital were referred to dermatology OPD for dermatological examination irrespective of any clinical symptoms related to skin disease.

Results – Out of total 212 patients diagnosed as chronic kidney disease (CKD) during evaluation of renal dysfunction in renal OPD 80 patients were detected to have definitive etiologies of CKD. In both Uddanam nephropathy (CKDu) and control group with known etiologies skin changes were predominant (more than 90% in both groups). Hair changes were least dominant with 23-30 % of populations affected. Xerosis was the commonest pattern (52-59%) followed by pigmentation, pruritus, ichthyosis. About 36 % of patients with CKDu and 35.1 % of the control group had involvement of nail, the majority of both groups have white nail followed by longitudinal ridges.

Limitations

The etiologies of chronic kidney disease were presumptive based on preceding history and investigations. Only a few cases were biopsy proven.

Conclusion- Skin manifestations are very common in CKD patients. There was no significant difference in dermatological manifestations between Uddanam nephropathy group and other groups of chronic kidney disease of known etiologies.

KEYWORDS : Chronic kidney disease of unknown etiology(CKDu); Chronic kidney disease(CKD); End Stage Renal Disease(ESRD); Hemodialysis(HD); Acquired perforating dermatosis (APD)

INTRODUCTION

An increased prevalence of chronic kidney disease (CKD) has been observed in several geographical areas across the world over the past two decades including Uddanam region in India. Uddanam endemic nephropathy is prevalent in the region of Uddanam, a lush green region in Srikakulam district, Andhra Pradesh of India and is considered as nephropathies of unknown etiology. This nephropathy is the least understood and the least publicized [1]. The association of specific occupations with endemic nephropathy has given importance to the issue of environmental toxins and heat stress, however, the cause of Uddanam nephropathy is still an enigma. A broad range of cutaneous manifestations occurs in chronic kidney disease patients. The severity of these manifestations ranges from the benign and asymptomatic to the physically disabling and life -threatening which may negatively impact on quality of life. As the renal functions deteriorate the incidence and prevalence of associated skin diseases also increase. Many of the cutaneous disorders experienced by patients undergoing dialysis have little to do with the uremic syndrome and are related to the underlying pathologic process that induced the renal disease. As reported in literature 50-100 % patients have the identifiable dermatological disorder and 41% patients have specific manifestations related to the disease [2,3]. The aim of the study was to identify common dermatological manifestations in chronic kidney disease patients of Uddanam region i.e. chronic kidney disease of unknown etiology (CKD u) after excluding other possible etiologies of renal dysfunction and to compare it with the patients of renal dysfunction with known etiologies.

MATERIALS AND METHODS

The study was done in a tertiary care hospital located in Andhra Pradesh, India. The dependent population of chronic kidney disease consists patients of Uddanam region of Andhra Pradesh India. This was an observational study from 02 Jan 2017 to 31 Dec 2017 done by Renal Clinic under the Department of Medicine. All the chronic kidney disease patients attending nephrology outpatient department (OPD) and patients undergoing regular dialysis in the hospital were referred to dermatology OPD for dermatological examination irrespective of any clinical symptoms related to skin disease. Persons residing in Uddanam region temporarily but belonging to other states were excluded. The approval of the hospital ethics committee was taken.

AIM OF THE STUDY –

To identify common dermatological manifestation in chronic kidney disease patients of Uddanam region (CKD u) after excluding other possible etiologies of renal dysfunction and to control with patients of renal dysfunction with known etiologies.

Inclusion criteria-

1. More than 18 yr of age
2. Renal dysfunction was defined if serum creatinine was >1.5 mg/dl which was confirmed after 1 week and 3 months
3. Any dialysis-dependent patients
4. Patients should be native of Uddanam region of district Srikakulam, Andhra Pradesh, India

Exclusion criteria

1. Patients belonging to regions other than Uddanam area
2. If raised serum creatinine normalizes after 1week or 3 months
3. Any aggravating illness/ drugs/other systemic diseases which can explain renal dysfunction.

All the patients with renal dysfunction included in the study underwent a thorough clinical evaluation. Routine investigations including hematological and biochemical investigations were carried out. Urine RE/ME, Spot Urine creatinine ratio, 24 hr urinary protein if Urine RE/ME showing > Protein 1+, HbA1C, Urea, Creatinine, sodium, Potassium, Calcium, Phosphorus, Lipid profile, Liver function test (LFT) with enzymes, intact parathyroid hormone (PTH), Electrocardiogram (ECG), Ultrasonography Kidney Ureter Bladder (USG KUB), and renal Doppler were done. Urea, creatinine, Urine RE/ME were repeated after 1 week and thereafter 3 months for confirmation of renal dysfunction for inclusion in the study. All the patients underwent fundus evaluation in Eye OPD by an ophthalmologist. Other tests like 2 D Echo, Chest X ray posterior anterior (CXR PA) view, High resolution computed tomography/ Contrast enhanced computed tomography (HRCT /CECT) chest, Non contrast computed tomography (NCCT) KUB, DTPA /DMSA scan, autoimmune makers (ANA, Anti dsDNA, C3, ANCA) were done on a case to case basis if indicated. Serological tests for HIV, HBsAg, Anti HCV were done in all patients. Culture and sensitivity of pus discharge from the lesion to exclude bacterial infections and potassium

hydroxide wet mount preparations to exclude fungal infections were performed. Skin biopsy for histopathological examinations of skin lesions was performed if indicated.

Statistical analysis was performed using SPSS version 20. A p value less than 0.05 was considered statistically significant.

RESULTS-

Total 212 patients were diagnosed chronic kidney disease (CKD) during evaluation of renal dysfunction in renal OPD and out of these 80 patients had definitive etiologies of CKD like DM-2, HTN, ADPKD, Nephrolithiasis, Glomerulonephritis etc and were treated as the control group. Only those 132 patients were included in Uddanam nephropathy group who had features suggestive of chronic tubulointerstitial disease in form of shrunken kidney sizes on USG, bland urine segment, nil proteinuria and had no features suggestive of any definitive etiologies of CKD.This group was provisionally classified as chronic kidney disease of unknown etiology (CKDu). Among 132 patients in CKDu, 87 patients (66%) were male and 45 patients (34%) were females. The age distribution of the patients ranged from 24-86 yrs with a mean age of 54.6 +_ SD 14.40 yrs. Majority of the patients were in the 40-59 yr group (52 %). The demographic profile of both groups is in Table 1. In control group 67.5% were male and 32.5% were female with duration of kidney disease 6-94 months. Majority of patients in control group with known etiologies were diabetic (See Table 2). If the study population was grouped as per CKD stage wise, with the severity of renal dysfunction percentage of population with cutaneous manifestations also increased. Almost all CKDu patients with CKD5D had some dermatological manifestations as compared to 88.8 % in patients with known etiologies. In CKD stage 4 of CKDu, about 82 % had dermatological manifestation as compared to 58.3% of control group which was statistically significant. In other CKD stages, population affected were comparable in both groups (See Table 3). In both CKDu and control group with known etiologies skin changes were predominant (more than 90% in both groups). Mucosal changes and nail changes were about 35-40 %. Hair changes were least dominant with 23-30 % of populations affected (See Table 4). Involvement of lower limb was more as compared to upper limb followed by trunk, scalp and genital regions (Table 5). Xerosis was the commonest pattern (52-59%) followed by pigmentation, pruritus, ichthyosis. The pattern of cutaneous manifestations in both the groups were comparable (Table 6). Few patients were also biopsied for definitive diagnosis of cutaneous lesions. 3 patients of Uddanam nephropathy and one diabetic patient were detected to have acquired perforating dermatosis (Table 7). About 36 % of patients with CKDu and 35.1 % of the control group had involvement of nail, the majority of both groups have white nail followed by longitudinal ridges. In the control group onychomycosis was more (14.8%) as compared to CKDu (6%) (Table 8). Buccal mucosa hyperpigmentation was the predominant oral mucosal lesion followed by scrotal tongue and furred tongue (Table 9).

Table 1. Demographic profile of patients

	CKD u	Control group (CKD of definitive etiology)
Total no. of patients – 212	132	80
Sex	Male- 87 (66 %) Female – 45 (34%)	Male- 54 (67.5%) Female- 26 (32.5%)
Age distribution	24-86 yr	32-76 yr
Mean age	54.6 +_ SD 14.40 yrs	48+_16.46 yrs
CKD Stage wise	CKD 3 -54 (40.9%) CKD 4- 34 (25.7%) CKD5 ND - 18 (13.6%) CKD 5D -26 (19.6%)	CKD 3-36(45%) CKD 4-12(15%) CKD5 -14(17.5%) CKD5D-18(22.5%)
Duration of kidney disease (months)	3-112 months Mean 10 +_ SD 16.62	6- 94 months Mean 12 +_ SD14.42
Duration of dialysis in dialysis dependent patients (months)	1-36 months	2-46 months

Table 2 . Etiology of CKD in control group i.e CKD of known etiology

Etiology	Male (54 patients)	Female (26 patients)
Hypertension	8 (14.8%)	4 (15.38%)
Diabetes mellitus Type 2	22(40.7%)	6 (23.07%)
Hypertension + DM-2	12(22.2%)	4 (15.38%)
ADPKD	2 (3.7%)	2(7.6%)
Chronic Glomerulonephritis	8(14.81%)	5(7.6%)
Nephrolithiasis	2 (3.7%)	1(3.8%)

Table 3. Dermatological manifestations CKD stage wise

CKD stage	CKDu (Affected/Total no)	Control group (Affected /Total no)	p value by t test
CKD stage 3	30/54 (55.5%)	20/36(55.5%)	P=0.32
CKD stage 4	28/34 (82.35%)	7/12 (58.3%)	P=0.012
CKD stage 5ND	16/18 (88.8%)	11/14 (78.5%)	P=0.398
CKD stage 5D	26/26 (100%)	16 /18((88.88%)	P=0.356
Total	100/132 (75.75%)	54/80(67.5%)	P=0.412

Table 4. Comparasion of dermatological manifestations

	CKDu	Control group	P value by t test
Skin changes	94/100 (94%)	54/54 (100%)	P=0.43
Nail changes	36/100(36%)	19/54(35.1%)	P=0.67
Mucosal changes	38/100 (38%)	22/54(40.7%)	P=0.64
Hair changes	23/100 (23%)	16/54 (29.6%)	P=0.53

Table 5. Skin Involvement of body portions

Body portions involved	CKD u	Control Group	P value by t test
Upper limb	76/94 (80.8%)	39/54(72.22%)	P=0.76
Lower limb	88/94 (93.61%)	48/54(88.88%)	P=0.64
Scalp	23/94 (24.4%)	13/54(24.07%)	P=0.34
Trunk	56/94 (59.57%)	33/54(61.1%)	P=0.86
Genital regions	19/94 (20.21%)	11/54(20.3%)	P=0.22

Table 6. Pattern of cutaneous manifestations

	CKDu	Compare group	P value
Xerosis	49/94 (52.1%)	32/54(59.2%)	0.42
Pigmentation	43/94 (45.74%)	28/54(51.8%)	0.315
Pruritus	38/94(40.42%)	23/54(42.59%)	0.236
Icthysois	23/94(24.46%)	19/54(35.18%)	0.432
Infectious diseases	12/94(12.76%)	7/54(12.96%)	0.126
Others	9/94 (9.57%)	5/54(9.25%)	0.132

Table 7. Diagnosis of other cutaneous manifestations

	CKD u (9 patients)	Control group (5 patients)	Remarks
Lichen planus	1	2	
Lichen Simplex chronicus	2	1	Biopsy proven
Seborrhoeic keratosis	2	1	
Acquired perforating dermatosis	3	1	Biopsy proven
Bullous lesions	1	0	

Table 8. Patterns of nail changes

	CKDu (36 patients/100 patients)	Control group (19 patients/54 patients)
White nail	18 (18%)	9 (16.6%)
Longitudinal ridges	12(12%)	7(12.9%)
Onychomycosis	6 (6%)	8(14.81%)
Half and half nail	8 (8%)	4 (7.4%)
Subungual hyperkeratosis	7 (7%)	3(5.55%)
Transverse ridging	5 (5%)	2(3.7%)
Clubbing	2 (2%)	1(1.85%)
Pitting	2 (2%)	1(1.85%)

Table 9 . Oral mucosal changes

	CKDu (38/100 pts)	Control group (22/54 pts)	P value
Buccal mucosa hyperpigmentation	23 (23%)	16(29.6%)	0.21
Scrotal tongue	7(7%)	4(7.4%)	0.376
Furred tongue	5(5%)	3(5.55%)	0.431
Candidiasis	2(2%)	1(1.85%)	0.183
Submucosal fibrosis	4(4%)	3(5.55%)	0.124
Angular cheilitis	8(8%)	5(9.2%)	0.332

Table 10. Infectious cutaneous manifestations

	CKDu (12/94 pts)	Compare group (7/54 pts)
Cellulitis	5(5.3%)	3
Infected wound	2	1
Sebaceous cyst infections	1	0
Fistula site infections	1	0
Herpes zoster	2	1
Fungal infections	3	5

DISCUSSION-

Chronic kidney disease patients have two main categories of cutaneous manifestations- Nonspecific and specific. Non-specific disorders include pigmentary disorders, pruritus, xerosis, acquired ichthyosis, and nail changes. Specific disorders include acquired perforating dermatosis, calciphylaxis, bullous dermatoses, and fibrosing dermopathy of uremia. It has also been proposed that changes in skin histology were more related to the severity and duration of the renal failure and less with its underlying etiology[4,5]. Xerosis, hyperpigmentation, pruritus, ichthyosis were the four most common manifestations in our patients which was consistent in other studies [6-10]. In our study xerosis was reported as 52-59% with no significant difference between CKD u and control group. Amatya et al [6] had reported xerosis in 28 % of patients while Khanna et al [7] and Shreshtha et al [10] in 72 % and 52% of patients respectively. Significant xerosis has been reported in 50–75% of the dialysis population[11]. There was a positive correlation between xerosis and pruritus which was reported by Khanna et al [7] to the extent of 87 %. In our study, about 84 % of patients in CKD u and 81 % in the control group had reported pruritus with xerosis. Lowered hydration of stratum corneum in the uremic patient with pruritus and dry skin promote the sensation of itch by lowering the threshold of itch [12]. Majority of patients (>80%) have an exacerbation of pruritus during sleep. It may be due to the physiological changes with diurnal rhythm and could be related to the expression of the diurnal rhythm of peptides and their receptors in the skin[13].

A spectrum of pigmentary alterations has been described in chronic kidney disease patients including pallor, brown-to-slate-gray discoloration, yellowish hue, and brownish hyperpigmentation in sun-exposed areas. A large number of uremia-related changes are responsible for cutaneous pigmentary changes[14]. In our study cutaneous pigmentation was observed in 45.74% in CKDu group while 51.8% in control group which was not statistically different. Pigmentary alterations were observed in 25–70% of dialysis population and increases over the duration of renal disease [15]. Pico et al. [2] reported that 70% of 102 dialysis patients manifested cutaneous pigmentary alteration. Shrestha P et al. [3] reported cutaneous pigmentation in 33 % of patients out of which 22 % had diffuse hyperpigmentation on sun exposure and 10% had generalized pigmentation. This hyperpigmentation is due to an increase in melanin production due to an increase in the poorly dialyzable beta melanocyte stimulating hormone [16]. The intensity of melanin pigmentation increases with respect to the duration of renal dysfunction and the duration of hemodialysis. The yellowish skin color has been attributed to retained liposoluble pigments such as lipochromes and carotenoids which are deposited in the dermis and the subcutaneous tissue[17]. The brown-to-slate gray discoloration noted in conjunction with dialysis dependent population has been attributed to hemosiderin deposition. It was also suggested that increased prevalence of diffuse hyperpigmentation with sparing of the sun-protected site could be due to tropical climate and sun exposure [7].

The infectious cutaneous manifestations were 12.76 % in CKDu group while it was 12.96 % in control group in our study. Silverberg et al [8] reported 70 % of patients with chronic kidney disease having infectious cutaneous manifestations. In our study infectious complications were few. Amartya et al [6] reported only 5 infectious cutaneous lesions out of 104 cases. In our patients acquired perforating dermatosis was present in three patients in CKDu group and one patient in the control group. In North America, the reported incidence of acquired perforating disorders (APD) varies from 4.5 to 10% of patients receiving maintenance hemodialysis[18]. A similar incidence of 11% has been recently reported in Britain [19]. The abundance of polymorphonuclear neutrophil remnants in the early stages of these disorders has led to the cellular dissolution of neutrophils with proteolytic enzyme release, including collagenase and elastase elaboration and it may initiate the pathologic process[20]. Fibronectin is chemotactic for neutrophils and is also capable of inciting epithelial migration and proliferation and it was postulated that dermal matrix deposition of fibronectin could be responsible for the disease process [21]. Both diabetes mellitus and ESRD have been shown to be associated with elevated serum fibronectin. Other proposed mechanisms of perforating dermatosis include defects in vitamin A or D metabolism associated with renal disease capable of inducing faulty epithelial proliferation and differentiation[22,23]. Metastatic calcification and nephrogenic systemic fibrosis were absent in CKDu and control group in our study. Similarly, in another study no metastatic calcification, acquired perforating dermatosis, bullous dermatosis was observed[24].

White nail (18%), longitudinal ridges (12%), onychomycosis (6%), half and half nail (8%) were the most common nail changes in our study which was comparable to the control group. This was consistent with the study by Shreshtha et al. [10]. Half and half nail was reported as high as 40 % by Pico et al [2] and as low as 4 % by Amatya et al. [6]. Half and half nail increases in prevalence with the duration of hemodialysis. In our study, only 19-22 % patients were dialysis dependent and dialysis vintage is not so prolonged explaining less prevalence of half and half nail - 8% in CKDu and 7.4 % in control group.

Buccal mucosa hyperpigmentation was very common in our study – 23 % in CKDu and 29.6 % in control group. Oral mucosal changes observed in 22% of cases by Shreshtha et al [10] and 24 % by Hajheyadri et al [24]. The pattern of mucosal changes was buccal mucosal hyperpigmentation (23%), scrotal tongue (7%), furred tongue (5%), angular cheilitis (8%). Hair changes were 23 % in CKDu group while 29.6 % in control group in our study. In another study, it was observed in 12 % cases [10] and 50 % cases [24]. Diffuse alopecia was reported resulting from telogen effluvium due to heparin use in a hemodialysis patient [7].

CONCLUSION –

Dermatological manifestations were as common in CKDu i.e. Uddanam nephropathy group as to control group cases of defined etiologies. Presence of dermatological problems in absence of primary dermatological disorder requires evaluation for kidney diseases. Skin, nail, oral mucosa and hair changes are very common in both Uddanam nephropathy and in renal dysfunction due to other etiologies. It also stresses the fact that most of the cutaneous manifestations in chronic kidney disease have nothing to do with the underlying pathologic process that induced the renal dysfunction.

Limitations

The etiologies of chronic kidney disease were presumptive based on preceding history and investigations. Only few cases were biopsy proven. Diagnosis of Uddanam nephropathy was considered if patients residing in Uddanam region had features suggestive of the chronic tubulointerstitial disease.

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