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## CKD of Unknown Origin in Supebeda, Chhattisgarh, India



Prawash Chowdhary<sup>1</sup>, Vinay Rathore<sup>2</sup>, Kamlesh Jain<sup>3</sup>, Abhiruchi Galhotra<sup>4</sup>, Nirmal Verma<sup>3</sup>, Sanjeev Anant Kale<sup>1</sup>, Nitin M. Nagarkar<sup>5</sup> and Vivekanand Jha<sup>6,7,8</sup>

<sup>1</sup>Department of Nephrology, Ram Krishna Care Hospital, Raipur, India; <sup>2</sup>Department of Nephrology, All India Institute of Medical Sciences, Raipur, India; <sup>3</sup>Department of Community Medicine, Pt. Jawaharlal Nehru Medical College, Raipur, India; <sup>4</sup>Department of Community and Family Medicine, All India Institute of Medical Sciences, Raipur, India; <sup>5</sup>All India Institute of Medical Sciences, Raipur; <sup>6</sup>George Institute for Global Health, New Delhi, India; <sup>7</sup>School of Public Health, Imperial College, London, UK; and <sup>8</sup>Manipal Academy of Higher Education, Manipal, India

**Correspondence:** Vinay Rathore, Department of Nephrology, All India Institute of Medical Sciences, Raipur, Chhattisgarh, India. E-mail: [vinayrathoredm@aiimsraipur.edu.in](mailto:vinayrathoredm@aiimsraipur.edu.in)

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Chronic kidney disease (CKD) is predominantly caused by diabetes, hypertension, and glomerular diseases. Nephrotoxic drugs, herbal medications, toxins, and infection are other causes of CKD in developing countries.

A clustered increase in prevalence of CKD has been observed in select geographic areas in several countries over the past 2 decades.<sup>1</sup> The etiology of CKD cannot be attributed to the known or traditional risk factors or causes, and the term chronic kidney disease of unknown etiology (CKDu) has been used to describe this entity.<sup>2</sup> Young males belonging to agricultural communities comprise the most common affected demographic. In India, this condition has been described from coastal villages of Srikakulam district in Andhra Pradesh and parts of Odisha.<sup>3, S1</sup> A variety of hypotheses including prolonged dehydration leading to heat stress, heavy metal toxicity, pesticide exposure, snake bite and genetics have been proposed.<sup>1</sup>

Recent media reports have highlighted an unusually high number of the deaths due to kidney disease in the tribal village or Supebeda in the Indian state of Chhattisgarh (Supplementary Figure S1).<sup>4</sup> Twelve patients from this village with kidney dysfunction were referred to 2 hospitals in Raipur between November 2019 and March 2020. In this report, we describe the clinical

presentation of these patients and present results of select toxicological analyses (Supplementary Methods).

### CASE SERIES

The 12 patients in this series (Table 1) came from 9 families (Figure 1), and 8 (66.7%) were males. The median age was 46 (interquartile range: 16.5) years. A majority presented with weakness, body aches, and decreased appetite. None gave a history of edema, hypertension, diabetes, snakebite, or acute kidney injury. All the patients were or had been farmworkers and regularly used pesticides and fertilizers without protective equipment. Six (50%) were regular consumers of locally brewed alcohol, and 7 (58.8%) were tobacco users. All had used herbal and ayurvedic medications. Most patients were poor and uneducated. The predominant cereal used by these patients was rice, and the primary source of drinking water was communal shallow wells and hand pumps. The blood pressure was <140/90 mm Hg in 11 (91.7%) patients.

Table 2 shows the laboratory findings. Three (25%) patients each presented in stages 4 and 5 CKD, whereas 6 (50%) had stage 3 disease. The serum potassium level was low in 5 (41.7%) subjects, and 8 (66.6%) had hyperuricemia. Only 2 patients (16.7%) had

**Table 1.** Clinical profile of patients referred from Supebeda suffering from chronic kidney disease

Characteristics	Patient no.											
	1	2	3	4	5	6	7	8	9	10	11	12
Age (yr)	42	45	60	30	40	45	38	60	85	55	52	47
Sex	M	F	M	M	F	M	M	F	F	M	M	M
Educ.	P	I	P	P	I	I	P	I	I	I	C	S
Monthly family income (INR)	5000–10,000	<5000	<5000	<5000	<5000	<5000	<5000	5000–10,000	<5000	<5000	5000–10,000	<5000
Symptoms	Weakness, decreased appetite, body aches	Weakness, breathlessness	Weakness, decreased appetite	Weakness, decreased appetite body aches	Weakness, decreased appetite	Weakness, decreased appetite, body aches	Weakness, decreased appetite	Weakness, decreased appetite, burning, micturition	Decreased appetite, body aches	Weakness, decreased appetite	Decreased appetite, vomiting	Back and body aches
Regular alcohol consumer	Yes	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No
Tobacco use	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No
BMI	19.5	18.8	18.8	18.0	18.4	19.1	20.1	17.1	35.1	17.8	21.2	17.6
SBP	150	130	100	108	130	130	120	130	130	120	110	100
DBP	90	80	70	60	80	80	80	80	70	70	70	60

BMI, body mass index; DBP, diastolic blood pressure; F, female; I, illiterate; M, male; P, primary; S, secondary; SBP: systolic blood pressure.

hyperphosphatemia, whereas 6 (50%) had hypomagnesaemia. Urinary sediment was bland in all cases, and protein excretion was <500 mg/d in in 5 (41.7%) and 500–1000 mg/d in 6 (50.0%) subjects. Ultrasound revealed symmetrically contracted kidneys in 11 patients (91.7%).

Kidney biopsy was done in patients 4 and 6 (Table 3, Figure 2) and showed glomerulosclerosis, interstitial fibrosis, tubular atrophy (20%–25% in case 4 and 20% in case 6), chronic vasculopathy, periglomerular fibrosis, and ischemic changes. Immunostaining was uniformly negative.

The urine of 10 patients was evaluated for heavy metals (arsenic, cadmium, chromium, cobalt, copper, lead, manganese, mercury, nickel, selenium, thallium, and zinc). Five patients showed high chromium levels, 3 had high manganese, and 1 had high nickel level (Supplementary Table S1). Urinary fluoride levels were elevated in 10 subjects, 1 of whom (patient 12) had features suggestive of skeletal fluorosis (Supplemental Figure S2).

## DISCUSSION

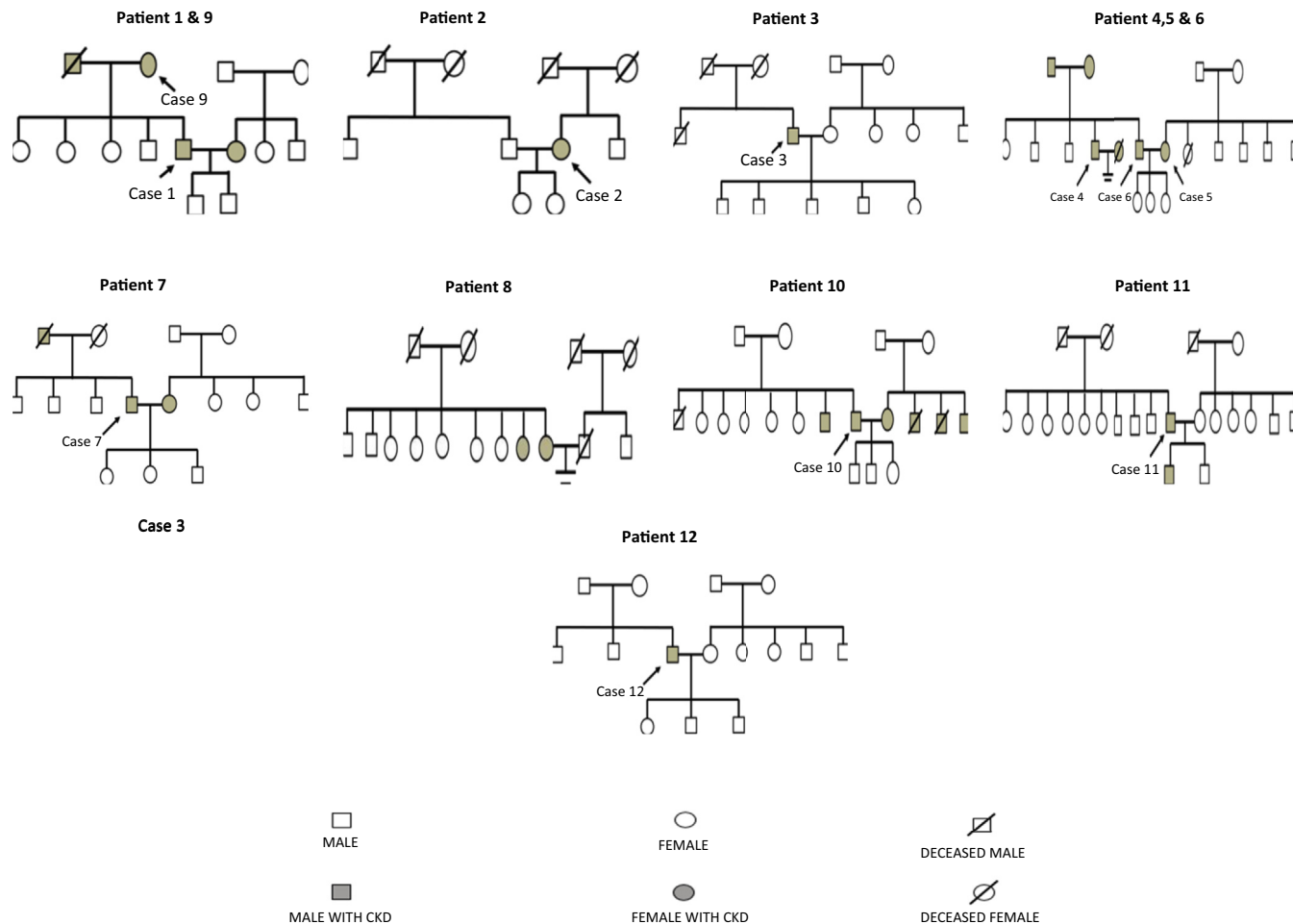
We describe a series of cases with CKD from a poor agricultural community in a village of the central Indian state of Chhattisgarh. The clinical characteristics of these cases bear similarities to the cases described of CKDu described from other parts of the world.<sup>1–3</sup> The similarities include absence of a known causes, such as diabetes, hypertension, prior glomerulonephritis or systemic disease, absent edema, normal or minimally raised blood pressure, low-grade proteinuria, bland

urinary sediment, and finding of smooth symmetrically contracted kidneys on ultrasound. Our workup, which was more extensive than that reported in the other studies from India, revealed some unusual findings: a higher than expected prevalence of hypokalemia and hypomagnesemia, normophosphatemia/hypophosphatemia and hyperuricemia, suggesting involvement of tubulointerstitial compartment. All the subjects were agricultural workers and came from poor socioeconomic background.

Although this is the first report of a cluster of cases from this part of India, it is possible that earlier cases were missed due to inadequate local health care services and lack of health-seeking behavior, preventing these cases from coming to nephrologist attention.

In India, CKDu has been reported from the states of Andhra Pradesh, Odisha, Goa, and Maharashtra.<sup>3,5</sup> In contrast to reports from Central America, Sri Lanka and Indian reports describe diagnosis at an older age<sup>1,2,3,6,S2</sup> and involvement in various agricultural activities, including paddy cultivation, cashew nut farming and roasting, and farm labor.<sup>1,3,5,S1,S2</sup> Most of our patients exhibited mild to moderate elevation in urinary protein excretion. There is no consensus on proteinuria cutoffs used for case definitions of CKDu. Some reports exclude those with urine protein excretion >500 mg/d, whereas others allow those with proteinuria of up to 3 g/day.<sup>3</sup> A significant proportion showed hyperuricemia, hypokalemia, and hypomagnesemia, the cause of which was not clear.

Renal histology in 2 patients showed chronic changes. All components of renal parenchyma were involved. The current histological descriptions of



**Figure 1.** Pedigree chart of patients referred from Supebeda suffering from chronic kidney disease.

CKDu emphasize tubular atrophy and interstitial fibrosis, which were limited to <30%. Vascular changes as seen in these two cases have not been described before. It was not possible to determine the

compartment where the injury started, and more work is needed in people at earlier stages of disease.

A majority of our patients were manual workers, engaged in outdoor work in a hot climate. A similar

**Table 2.** Laboratory parameters of patients referred from Supebeda suffering from chronic kidney disease

Parameter	Patient no.												
	1	2	3	4	5	6	7	8	9	10	11	12	
Hemoglobin (g/dl)	9.4	4.5	6.8	9.9	8.9	9.6	10.5	9.2	10.3	9.1	4.6	6.0	
Serum creatinine (mg/dl)	7.6	12.5	2.1	1.7	2.3	2.2	2.4	1.8	2.5	2.1	14.2	4.0	
eGFR (ml/min/1.73 m <sup>2</sup> )	8.0	3.0	33.0	53.0	26.0	35.0	31.0	30.0	17.0	34.0	3.0	15.0	
HbA1C	5.8	5.6	5.5	4.9	5.1	5.3	5.4	5.6	5.4	5.9	5.7	6.1	
Serum sodium (meq/l)	138	143	136	1437	139	136	135	138	137	136	109	118	
Serum potassium (meq/l)	4.37	3.06	4.8	3.3	4.1	3.6	3.6	3.1	3.4	4.2	3.36	4.2	
Serum uric acid mg/dl)	7.9	8.5	7.0	9.7	5.2	8.6	10.3	5.2	8.8	6.8	11.98	11.6	
Serum calcium (mg/dl)	7.4	7	8.0	8.5	9.5	9.2	9.2	8.3	9.0	10.0	8.69	9.17	
Serum phosphorus (mg/dl)	5.14	6.1	3.18	3.0	4.1	3.3	2.6	3.5	6.8	3.2	4.6	5.3	
Serum magnesium (meq/l)	1.69	1.7	1.32	1.58	1.91	1.38	1.49	1.51	1.81	1.71	1.6	1.9	
Serum bicarbonate (meq/l)	18	10	19.6	20.8	20.8	19.8	17.1	28.3	19.6	17.6	14.2	16.3	
Serum albumin (g/dl)		2.9	2.7	3.6	3.6	3.5	2.8	3.3	3.6	3.6	3.5	3.8	
24-h urinary protein (mg)	243.2	918.6	615	1000.2	862.5	939.2	456.6	302.4	356.7	794.4	426.2	523.3	
Urine-specific gravity	1.001	1.01	1.005	1.01	1.005	1.005	1.015	1.01	1.01	1.005	1.001	1.001	
Kidney size (cm)	Right	8.4	7.9	7.4	9.2	8.0	8.7	6.7	8.5	8.3	5.6	7.6	7.2
	Left	8.7	7.0	6.2	9.5	8.0	8.0	6.9	8.4	8.5	6.6	7.2	7.1

eGFR, estimated glomerular filtration rate, calculated by CKD-EPI formula.<sup>58</sup>

**Table 3.** Renal biopsy findings of patients 4 and 6

Characteristics	Patient 4	Patient 6
Light microscopy		
Number of glomeruli	6	13
Glomeruli	4 sclerosed; others show periglomerular fibrosis and ischemic changes in the underlying tuft	8 sclerosed; others show periglomerular fibrosis and ischemic changes in the underlying tuft
Tubules and interstitium	IFTA: 20%–25%, chronic interstitial inflammation	IFTA: 20%, chronic interstitial inflammation
Blood vessels	Focal hyalinosis and vacuolization of smooth muscle cells of media	Medial thickening and fibrointimal sclerosis
Immunofluorescence microscopy		
	Negative staining for IgG, IgA, IgM, C1q, kappa and lambda light chains, trace staining for C3	Negative staining for IgG, IgA, IgM, C3, C1q, kappa and lambda light chains
Electron Microscopy		
	Basement membrane Thickness: 288.9–611.5 nm, no deposits in basement membrane or mesangium, no tubuloregular inclusions	Basement membrane Thickness: 281.6–641.2 nm, no deposits in basement membrane or mesangium, no tubuloregular inclusions

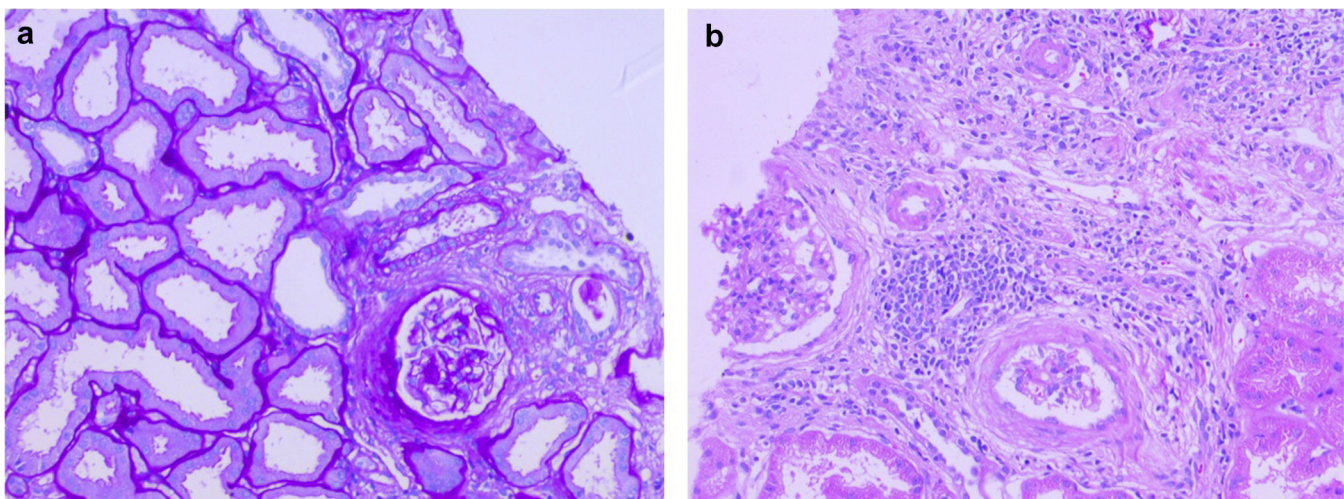
IFTA, interstitial fibrosis and tubular atrophy; Ig, immunoglobulin.

profile has been described in reports of CKDu from other places.<sup>1,2,5,6</sup> Prolonged dehydration, analgesic abuse, genetics, pesticide exposure, and contamination of drinking water with heavy metals in water have been suggested as possible causes of CKDu.<sup>1,51</sup> An interesting finding was the history of kidney disease in 6 of the 9 families. Most of the affected family members were first-degree relatives, but spousal involvement was also noted. Although it may point to a genetic etiology, exposure to a shared environmental insult is equally plausible.

Urinary toxicological screen showed some abnormalities, but the levels of heavy metals that have been most frequently implicated in causation of kidney disease (arsenic, cadmium, mercury, and lead) were within normal range.<sup>7</sup> Recent environmental studies have not found heavy metals to be associated with CKDu.<sup>53–55</sup> All patients had elevated urinary fluoride, and 1 showed radiological evidence of skeletal

fluorosis. Fernando *et al.* reported elevated serum and urinary fluoride levels in patients suffering from CKDu from Sri Lanka.<sup>8</sup> This finding, however, needs to be interpreted in light of the reduced GFR. Measurement of serum/tissue levels might provide better understanding of the load. Pesticides have been postulated as a causal factor.<sup>56</sup> Our patients reported using pesticides without protective equipment. However, this practice is widespread in India and hence unlikely to be the sole cause of kidney disease. Even though we focused on a possible toxic etiology of kidney disease, the role of undiagnosed glomerulonephritis in the past or low birth weight in the causation of CKD cannot be ruled out.

In conclusion, this is the first report of patients with possible CKDu from a new region in India. Detailed epidemiological study is needed in the village and the surrounding area to define the disease burden and elucidate causal factors.



**Figure 2.** Kidney biopsy of patients 4 and 6. (a) Light microscopy finding of kidney biopsy of patient 4 showing periglomerular fibrosis (PAS stains, original magnification  $\times 40$ ). (b) Light microscopy finding of kidney biopsy of patient 6 showing focal periglomerular fibrosis with tubular atrophy and chronic interstitial inflammation (H&E stains, original magnification  $\times 40$ ).



## DISCLOSURE

VJ has received grant funding from GSK, Baxter Healthcare, and Biocon and honoraria from NephroPlus and Zydus Cadilla, under the policy of all honoraria being paid to the organization. All the other authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

## Supplementary Methods.

**Table S1.** Urine toxicology evaluation of patients by inductively coupled plasma mass spectrometry.

**Figure S1.** Map showing the location of Supebeda.

**Figure S2.** X-ray of forearm and leg of patient 12 showing interosseous calcification suggestive of skeletal fluorosis.

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## Long- Versus Short-Acting Erythropoiesis-Stimulating Agent Type and Mortality



Angelo Karaboyas<sup>1</sup>, Friedrich K. Port<sup>1</sup>, Ziad A. Massy<sup>2</sup>, Francesco Locatelli<sup>3</sup>, Aleix Cases<sup>4</sup>, Kosaku Nitta<sup>5</sup>, Sophie Liabeuf<sup>6</sup>, Kitty J. Jager<sup>7</sup> and Bruce M. Robinson<sup>1,8</sup>

<sup>1</sup>Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA; <sup>2</sup>Ambroise Paré University Hospital, Assistance publique Hôpitaux de Paris, Department of Nephrology Boulogne-Billancourt/Paris, and Institut national de la santé et de la recherche médicale Unit 1018, Team 5, CESP, Saclay University, and Versailles Saint-Quentin-en-Yvelines University, Paris-Ile-de-France-West University, Villejuif, France; <sup>3</sup>Alessandro Manzoni Hospital, Department of Nephrology, past director, ASST Lecco, Lecco, Italy; <sup>4</sup>Universitat de Barcelona, IDIBAPS, Barcelona, Spain; <sup>5</sup>Department of Nephrology, Tokyo Women's Medical University, Tokyo, Japan; <sup>6</sup>Pharmacology Department, Amiens University Hospital and MP3CV Laboratory, EA7517, University of Picardie Jules Verne, Amiens, France; <sup>7</sup>ERA-EDTA Registry, Department of Medical Informatics, Amsterdam UMC, Academic Medical Center, Amsterdam Public Health Research Institute, University of Amsterdam, Amsterdam, the Netherlands; and <sup>8</sup>University of Michigan, Department of Internal Medicine, Ann Arbor, Michigan, USA

**Correspondence:** Angelo Karaboyas, Arbor Research Collaborative for Health, 3700 Earhart Rd, Ann Arbor, MI 48105, USA. E-mail: [Angelo.Karaboyas@ArborResearch.org](mailto:Angelo.Karaboyas@ArborResearch.org)

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Most patients with end-stage kidney disease (ESKD) who are undergoing maintenance hemodialysis (HD) are affected by anemia and receive erythropoiesis-stimulating agents (ESAs) to maintain

hemoglobin levels in the target range. Long-acting ESAs, such as darbepoetin and epoetin beta pegol, have a longer half-life and thus can be administered less frequently than short-acting ESAs, such as epoetin