Renal Cortical Necrosis: A Rare but Roaring Entity in Acute Kidney Injury Patients

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Abstract

Background: Renal cortical necrosis (RCN) is a fatal variety of kidney disease with adverse outcomes. RCN accounts for two percent of all AKI (Acute kidney injury) patients from developed countries. There are number of published studies in the literature describing Renal cortical necrosis in Acute Kidney Injury Patients. However, there is a lack of recent data on Renal cortical necrosis from India. The purpose of this study was to analyze the clinical profile, causes and outcome of Renal cortical necrosis in AKI patients.

Methods: All AKI (Acute Kidney Injury) Patients admitted during a period of 2 years were evaluated. Detail clinical profile of AKI patients including history and physical examination were studied. Complete blood count, renal function tests, Liver function tests, Urinalysis, Coagulation profile were done in all patients. Selected patients underwent Immunological assay. Patients suspected to have renal cortical Necrosis are advised to undergo Contrast Enhanced Computed Tomography scan of KUB and/or renal biopsy. Demography, clinical profile, causes and types of RCN, course in the hospital and Management aspects were studied in detail. Patients were followed up for 3 months to determine the recovery of renal function or progression to chronic kidney disease/ End stage renal disease.

Results: Among four hundred fifteen AKI patients (415), fifteen were found to have renal cortical necrosis with an incidence of 3.6%. Obstetric causes were the main cause of RCN in female patients and non-obstetric factors were the main causes in majority of male patients. Complete cortical necrosis was noted in 4 (26.6%) patients and remaining 11 (73.3%) patients had patchy cortical necrosis. Four (26.6%) patients were dialysis dependent at the end of 3 months and remaining were free from dialysis.

Conclusion: Abruptio placenta and Snake bite were the main causes of RCN. Oligoanuria was the main presenting complaint. Sepsis and DIC was seen in more than 50% of the patients. Progression to chronic kidney disease is common.

Keywords: Renal cortical necrosis, abruptio placenta, snake bite, septic abortion, chronic kidney disease.

Introduction

Renal cortical necrosis (RCN) is a severe and often irreversible form of ATN (Acute tubular necrosis). It is characterized by a total (complete) or subtotal (patchy) necrosis of the renal elements of cortex (glomeruli, blood vessels and tubules) of both kidneys, is perhaps the most catastrophic among all types of acute renal failure[1,2]. RCN usually results from the significant diminution of renal arterial perfusion due to vascular spasm and microvascular injury. The striking features of this condition are a prolonged period of oligoanuria and failure of complete recovery of renal function. Described for the first time in 1883 by Friedlander[3], RCN has been observed in association with a variety of conditions. Common obstetric causes of RCN are septic abortion, puerperal sepsis, abruptio placenta, eclamptic toxaemia, post- partum haemorrhage[4,5]. The non-obstetric conditions leading to acute cortical necrosis are: extensive burns, pancreatitis, septicaemia, snake bite, and diabetic ketoacidosis[6,7]. RCN accounts for only 2% of all causes of acute renal failure[4]. Obstetric complications are the commonest

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(50-70%) cause of renal cortical necrosis[8,9] non-obstetric causes account for 20-30% of all cases of cortical necrosis and in these circumstances the incidence is higher in men than in women[10]. The purpose of this study was to analyze the clinical profile, causes and outcome of Acute renal cortical necrosis in AKI patients.

Material and methods

All AKI (Acute Kidney Injury) Patients attending to the department of Nephrology, Medicine and Obstetrics and Gynecology for a period of 2 years were evaluated. Meticulous clinical examination was carried in all cases. They were evaluated further using appropriate laboratory investigations to determine the cause of AKI individually such as Urine examination, complete blood count with peripheral smear, random blood sugar, serum lactate dehydrogenase, coagulation parameters (Prothrombin time, Activated partial thrombin time), renal function tests, liver function tests. Radiology examination (USG abdomen for Kidney size, margin, echogenicity, corticomedullary differentiation, associated lesions (hydronephrosis, calculus) was done in all cases. Immunological assays (ANA, AntidsDNA, C3,C4, ANCA, Antiphospholipid antibody) was done in selected patients. Contrast enhanced CT scan KUB and/or Kidney Biopsy in patients with prolonged AKI (oilgoanuria of more than 4 weeks) to look for the evidence of cortical necrosis. Then, the patients were divided into obstetrics and non-obstetric group. Demography, clinical profile, causes and types of RCN (complete v/s patchy), course in the hospital and Management aspects were studied in detail. Patients were followed up for 3 months determine the recovery of renal function or progression to chronic kidney disease/End stage renal disease. Study design: Cross sectional study. Inclusion criteria: All AKI (Acute kidney injury) patients who gave voluntary consent. Exclusion criteria: Patients who had not given voluntary consent, Patients with underlying kidney disease (chronic kidney diseases), obstructive uropathy. Consent: Written informed consent was obtained from each enrolled patient prior to their induction into the study. A detail history, review of case sheets, physical examination and laboratory investigations were conducted for each patient. Statistical Analysis: The data was analyzed using SPSS software and the results were recorded as mean, median and standard deviation.

Results

Four hundred and fifteen patients of AKI were evaluated during the study period. Among them, 15 patients were diagnosed to have Renal cortical necrosis with an incidence of 3.6%. Thus, RCN was noted in 1 in 28 AKI patients. The age of RCN patients ranged between 25 to 60 years, with mean of 37.9±13.3 years. Majority of RCN patients were females 10 (66.7%) and remaining were males 5 (33.3%) (Table 1). Obstetric patients contribute to 60% (nine) of total RCN patients and remaining 40% (six) of cases are non-obstetric (Table 2). In non- obstetric group, RCN was noted in 5 males and in 1 female patients. RCN occurred in 20% (three) of the patients in 1st trimester, 26.7% (four) in 3rd trimester and 13.3% (two) cases in postpartum period. In obstetric group common causes of RCN were Abruptio placenta in 4 (26.7%) cases followed by Septic abortion in 3 (20%) cases, Post-partum hemorrhage in 1 (6.7%) and puerperal sepsis in 1 (6.7%) patient (Table 3). In non- obstetric group, Snake bite was responsible for RCN in 26.7% (four) cases followed by Acute gastroenteritis in 6.7% (one) and Acute pancreatitis in 6.7% (one) of the patients (Table 3). Oligoanuria was the main presenting complaint with complete anuria in 5 (33.3%) of the patients and remaining 10 (66.7%) were oliguric. Oedema and icterus were the presenting complaints in 93.3% (fourteen) and 80% (twelve) of the patients respectively. Nine (60%) patients had hypotension at the time of admission. RCN patients had mean systolic blood pressure of 104.2±7.9 mmHg ranging from 70-160 mmHg and mean diastolic blood pressure of 66.4±3.6 mmHg ranging from 50 to 88 mmHg. 8 (53.3%) patients were febrile at admission. Among 15 RCN patients, 53.3% (eight) had a sepsis and platelets were low in 11 (73.3%) patients. The mean serum urea was 115±36 mg/dl, ranging from 60–170mg/dl, while serum creatinine ranging from 3.4-12.5 mg/dl, mean was 7.6±2.3. Levels of potassium were in the range of 3.6-6.8meq/L, mean was 5±0.8meq/L (Table.4). Coagulation parameters was deranged and D-dimer was elevated in 66.7% (ten) and 33.3% (five) of the patients respectively. Six (40%) patients had undergone renal biopsy. Of which 4 had complete cortical necrosis and 2 patients had patchy cortical necrosis (Figure 1). Contrast enhanced CT KUB was done in 9 (60%) patients. All of them showed patchy cortical necrosis (Figure 2). Of 15 RCN patients, 4 had complete cortical necrosis and remaining 11 had patchy involvement of the cortex (Figure 3). Eighty percent (twelve) of the patients were dialysis dependent at the time of admission and twenty percent (three) were managed conservatively. All fifteen patients were followed up for 3 months to see improvement in the renal function. Of 12 dialysis dependent patients, we saw partial improvement in renal function in 8 patients and were out of the dialysis. We didn't see any worsening of renal function in 3 conservatively managed patients. So, at end of

three months, 4 patients were dialysis dependent and remaining 11 patients were not requiring dialysis. We didn't see any improvement in renal functions of complete cortical necrosis patients, even though 8 patients of patchy cortical necrosis were dialysis dependent at the of admission, there was a partial recovery in the renal function and out of dialysis at the end of three months (Figure.4).

Table.1: Age & Gender distribution of study subjects

	N (Percent)	AGE (Years) Mean (SD)
Male	5 (33.33)	50.8 (9.88)
Female	10 (66.67)	31.5 (9.74)
Total	15 (100)	37.93 (13.33)

Table.2: Main Categories of RCN Patients in AKI patients. (n=15)

Categories	Number	Percentage
Obstetric	9	60%
Non-Obstetric	6	40%

Table.3: Main Causes of RCN in AKI Patients. (n=15)

Causes	Number	Percentage
Obstetric Causes		
1. Abruptio placenta	4	26.7%
2. Septic abortion	3	20%
3. Post-partum hemorrhage	1	6.7%
4. Puerperal sepsis	1	6.7%
Non-obstetric Causes		
1. Snake bite	4	26.7%
2. Acute Gastroenteritis	1	6.7%
3. Acute Pancreatitis	1	6.7%

Table.4: Severity of RCN in Acute Kidney Injury in patients. (n=15)

Parameters	Mean (SD)	Median (IQR)	Minimum	Maximum
Serum urea (mg/dl)	115.6 (36.15)	120 (88 - 145)	60.00	176.00
Serum creatinine (mg/dl)	7.63 (2.40)	7.9 (6.4 - 8.9)	3.40	12.50
Serum potassium (meq/L)	5.51 (0.83)	5.8 (4.8 - 6.1)	3.90	6.80

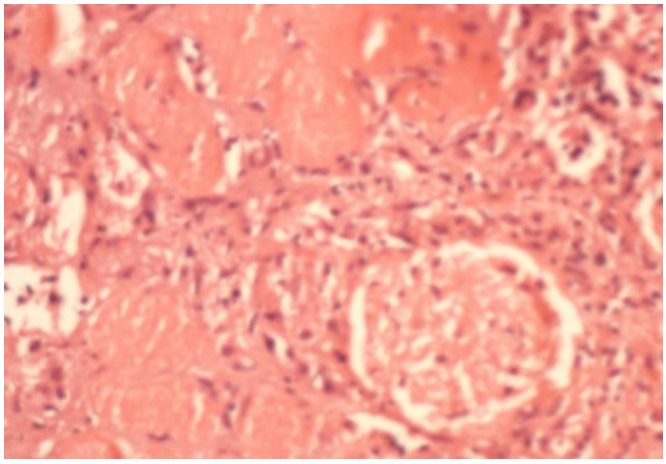

Figure 1. Shows Patchy necrosis of the Cortical elements

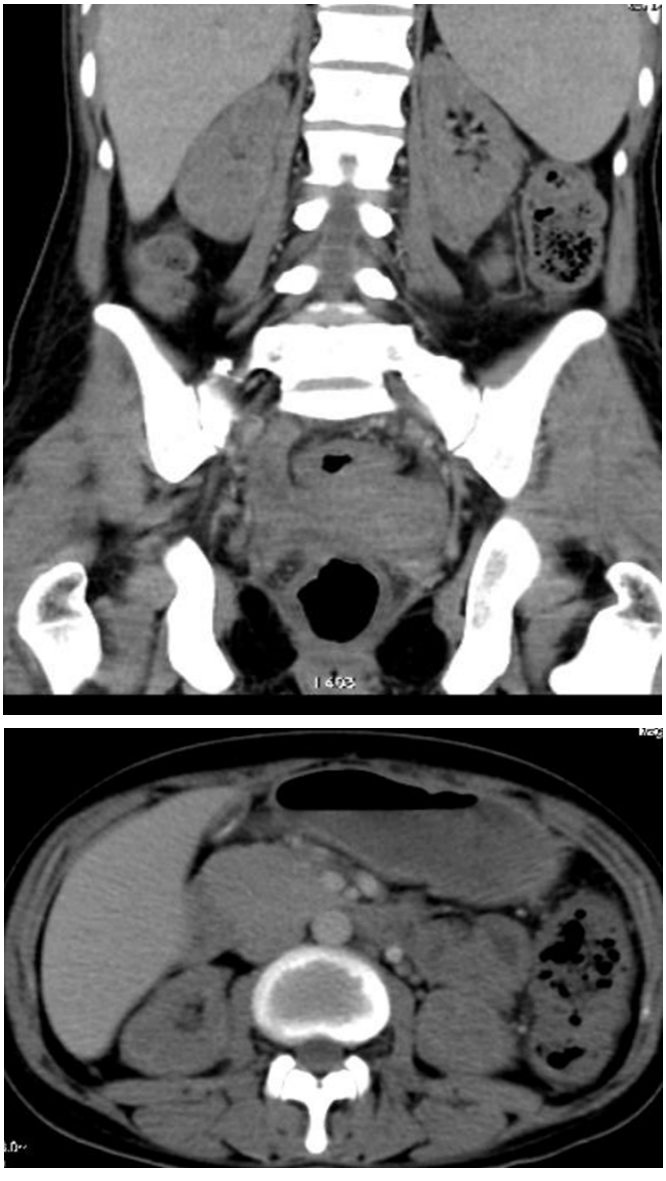

Figure 2. Cortical necrosis a (Axial) and **b (coronal)** CECT sections showing patchy enhancing and non-enhancing areas involving cortex with loss of corticomedullary differentiation.

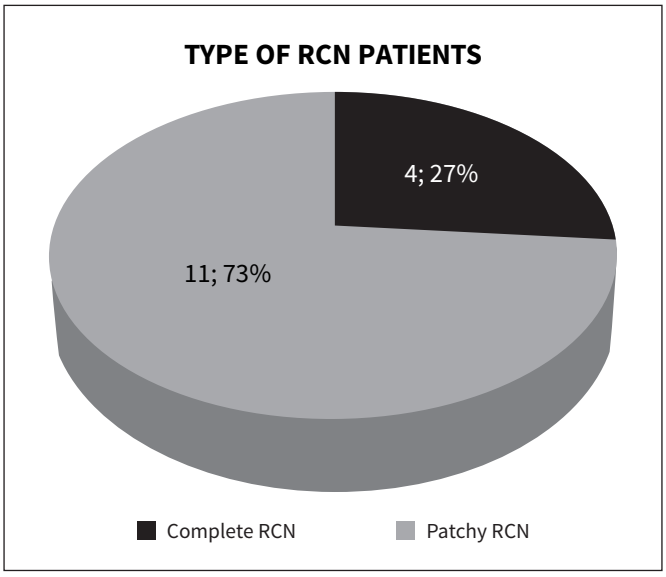

Figure. 3: Types of RCN (n=15)

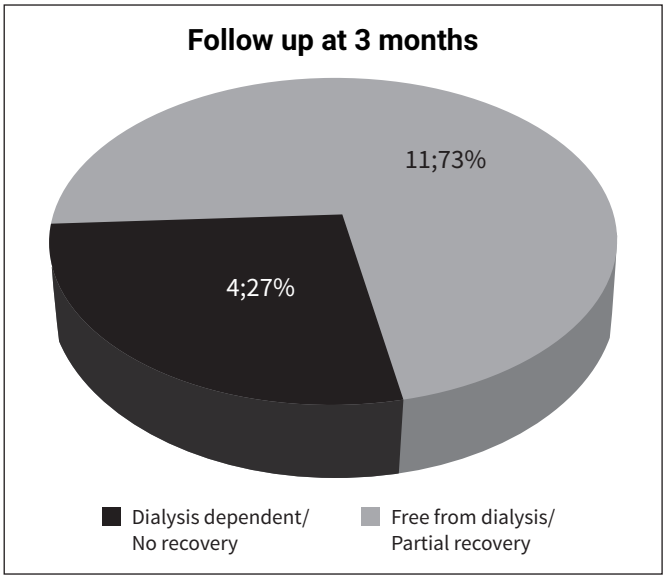

Figure.4: Dialysis dependency/ Recovery after 3 months of follow up(n=15)

Discussion

1. Incidence of RCN

RCN accounts for less than 2% of all cases of acute kidney injury (AKI) in developed countries[4]. While in developing countries, the incidence is in between 6%-7% of all causes of acute kidney injury (AKI)[11,12,13]. In an Indian study conducted by Prakash J et al, the incidence of RCN was 6.3% of AKI patients[11]. A study from Chandigarh had observed RCN in 7.1% of patients dialyzed for acute kidney injury[1]. The overall incidence of RCN has decreased to 1.6% (of total cases of acute renal failure) in 1995-2005 from 6.7% in 1984- 1994[14]. Liano and Pascual had observed RCN in only one case (0.13%) among 46 patients with renal biopsy in their series of 748 cases of AKI[15]. RCN is an extremely rare cause of AKI in Europe. These observations indicate that RCN incidence is still high in developing countries in comparison to Europe and North America. The higher incidence of RCN in developing countries, including India, is related mainly to AKI occurring during obstetric complication. However, we have observed RCN in 3.6% of total AKI patients. Thus, RCN was noted in one in twenty-eight AKI patients.

2. Causes of RCN

a. Obstetric causes:

Most common causes of RCN in obstetric patients are septic abortion, abruptio placentae, puerperal sepsis, eclampsia, obstetric haemorrhage, intrauterine death, and thrombotic microangiopathy of pregnancy (P-TMA)[4,16,17]. Overall, obstetrical causes are the dominant causes of RCN which account for 56%-61% of cases[14,18,19]. RCN was reported to occur in 10%-30% of all cases of pregnancy related AKI compared with approximately in 5% of non- pregnant women[15]. Of 57 patients with RCN; pregnancy-associated complication and nonpregnant condition were causative factor for RCN in 32 (52.2%) and 25 (43.8%) respectively[20]. Postabortal sepsis is a common cause of RCN in obstetric AKI in developing countries while, abruptio placentae is responsible for RCN in 50%-60% of case in pregnancy in developed countries[6,21]. This could be attributed to the abortions which are commonly conducted by unskilled persons mostly under unhygienic condition, which leads to higher incidence of post-aboral sepsis. It is postulated that endothelial injury due to endotoxins may cause endovascular damage and vascular thrombosis with consequent renal ischemia in patients with sepsis and septic abortion. RCN in placental abruption may be due to a combination of blood loss, hypercoagulable state, endothelial injury and intravascular thrombosis. We have observed obstetric causes were the most common causes of RCN in 60% (nine) of the patients in our study. Abruptio placenta was the main cause of RCN in 26.7% (four) of the patients followed by septic abortion in 20% (three), post- partum haemorrhage and puerperal sepsis in 6.7% (one) patients. This is in accordance with the developed countries where, abruptio placenta is commonest cause of RCN in obstetric patients.

b. Non- obstetric causes

Our present study had showed, RCN in 40% (six) of the cases in non-obstetric category of RCN. Snake bite was the most common cause in 26.7%

(four) of the patients followed by Acute severe gastroenteritis in 6.7% (one) and Acute haemorrhagic pancreatitis in 6.7% (one) of the total AKI patients. Earlier studies had shown that, the various causes for non-obstetrical causes of RCN were extensive burns, snake bite, sepsis, pancreatitis, HUS, infancy and childhood dehydration, malaria and drugs and toxin[14,18]. Non-pregnancy associated complication accounted for RCN in 34.8% of total AKI cases[17]. RCN was due to pregnancy and non-pregnancy related complications, in 56.2% and 43.8% cases respectively in a study by India[14]. HUS was the most common cause 18/25 (72%) of cortical necrosis in the non-obstetrical group[14]. Severe sepsis, extensive burns (80%), massive gastrointestinal haemorrhage, acute pancreatitis and diarrhoea associated shock are other causes of RCN in non-pregnant group[14]. Among the nonobstetric cases, envenomation by snakes of the viperine family constituted the largest group of patients developing RCN. 22% of all patients with viper bite induced acute renal failure showed RCN on renal biopsy or autopsy[22]. Development of RCN following snake bite has also been reported from other part of the world[23,24]. Haemolytic uremic syndrome is a common cause of acute renal failure in children and is usually associated with a gastrointestinal prodrome. Acute renal cortical necrosis is seen in up to 25% of these patients and is associated with a prolonged anuric phase and poor prognosis[25,26]. However, we have not noticed any case of HUS in our study, possibly because of occurrence of HUS is more common in children than Adults. Four previous reports have recorded the association between bilateral renal cortical necrosis and pancreatitis[27,28].

Sequestration of large amount of fluids or renal vasoconstriction as a result of release of vasoactive substances during pancreatitis has been postulated to cause AKI in these patients. Four patients had RCN in association with acute haemorrhagic pancreatitis. Two of them survived the initial episode but remained dialysis dependent.

3. Diagnosis of RCN

Initially, a definitive diagnosis of RCN was possible only on histologic examination of the renal tissue. Detection of a cortical tram-track or egg-shell calcification on plain x-ray of abdomen is cited as the hallmark of RCN. Renal cortical calcification has been recorded as early as 10 days after the onset of ARF; however, this is uncommon and the usual interval is 1-2 months after the acute event. Selective renal angiography has sometimes been used to make an early diagnosis[29]. The nephrogram is nonhomogeneous; mottled and striate in patchy, and absent in diffuse RCN. Other findings include prominent capsular vessels, delayed or incomplete filling of interlobular arteries, prolongation of circulation time, and rapid shunting of blood through the medulla with early venous filling. CECT scan of the kidneys proved to be a useful and specific modality for the early diagnosis of renal cortical necrosis[30] which shows (a) lack of enhancement of the renal cortex, (b) enhancement of the renal medulla, and (c) absent renal excretion. We have diagnosed 6 (40%) cases of RCN based on renal histology. Out of 6 cases 4 had complete cortical necrosis and remaining 2 had patchy involvement of the cortex. Contrast enhanced CT KUB was done in 9 patients, all of them showed patchy involvement of the renal cortex.

4. Types and outcome of RCN

RCN has been divided into two categories based on the histological criteria. i) Complete cortical necrosis: Confluent global cortical destruction extending into the columns of Bertin.

The thin rim of subcapsular and juxtamedullary tissue may be preserved. Irreversibility of renal function is the rule in complete cortical necrosis. (ii) Patchy cortical necrosis: Contiguous area of cortical necrosis involving one-third to half of the entire cortical tissue. This form has potential for partial recovery of renal function. We have observed complete cortical necrosis in 4 (2 septic abortion, 1 Abruptio placenta and 1 snake bite) (26.7%) patients and patchy involvement of cortex in remaining 11 (73.3%) patients. Out of 15 AKI patients, 12 (80%) were dialysis dependent at the of admission and 3 (20%) patients were managed conservatively. Among 12 dialysis dependent patients, 4 were having complete cortical necrosis, did not show any improvement in the renal function at the end of three months Remaining 8 patients showed some improvement in the renal function, were able to manage without dialysis. So, at the end of 3 months of follow up of RCN patients, 4 (26.7%) patients have reached ESRD (End stage renal disease) and 11 (73.3%) patients have chronic Kidney disease. We have observed that a permanent damage to the kidneys is a rule in RCN patients. Earlier study had showed diffuse in 41 (72%) and patchy cortical necrosis in 16 (28%) patients. Thirty (52.6%) patients died during the acute phase of the illness. Chronic renal failure occurred in 30–50% of patients requiring dialysis and transplantation. 11 (19.2%) patients with patchy cortical necrosis who had partial recovery of renal function and were dialysis independent. The remaining 16 (28%) patients progressed to end-stage renal disease (ESRD). Progression to ESRD was seen in a higher number of cases in the second period 10

(47.6%) in comparison with 6 (16.6%) patients who progressed to ESRD in the first period[14]. However, we have not noticed any mortality in our present study, possibly because of early detection and management of complications of acute kidney injury such as volume overload, hyperkalaemia and metabolic acidosis. The clinical course of patients with RCN can be divided into five broad groups: (1) death in uraemia during the acute phase; (2) survival without dialysis; (3) late return to dialysis/transplant; (4) survival only with chronic maintenance dialysis/transplant; and (5) late resumption of sufficient renal function to become dialysis independent. The causes of death during acute phase of illness are; severe uraemia, sepsis, pulmonary oedema, gastrointestinal haemorrhage and hyperkalaemia including multiorgan failure[14]. Survival without dialysis is possible in patients with patchy cortical necrosis because surviving nephrons carry the function of the remaining kidney. In certain patients, there may be slow rise in creatinine clearance and a gradual gain in renal function over one to two years, so that the glomerular filtration rate may reach a final plateau level of approximately 20-24 mL/min[31,32]. It is assumed that juxtamedullary glomeruli (which comprise 15%-20% of total) escape destruction, even in the complete cortical necrosis and that early functional return is due to recovery of these nephron segment. Possibly because of this, 8 of our patients showed some improvement in the renal function even though dialysis dependent at admission. The deterioration in renal function had been reported several years (1-10 years) after the acute cortical necrosis in a significant number of patients. Factors causing these late functional downturns are not clear but may include pyelonephritis, hypertension and shrinkage of the kidney due to progressive fibrosis and/ or calcification[33,34].

5. Pathophysiology of RCN

The sequence of pathophysiologic events in cortical necrosis remains unclear. A number of pathogenetic mechanisms have been postulated. The initiating event appears to be vasospasm of small vessels or liberation of toxins causing capillary endothelial damage[35,36]. It has been suggested that in pregnancy, the vasculature is more prone than usual to vasoconstriction, and a possible role of sex hormones has been proposed[36]. RCN also shares many similarities with the generalized Schwartzmann reaction induced in rabbits by endotoxin[37]. Whereas in nonpregnant animals, two small doses administered 24 h apart cause this phenomenon, only one injection is sufficient in pregnant rabbits[38]. Studies have shown the role of endothelin-1 in the development of RCN possibly by its potent vasoconstriction effects39. Renal vasculature appears to be 10 times more sensitive to this effect of endothelin- 1 compared to all other vascular organs. In addition, tissue ischemia has been shown to potentiate its vasoconstricting effect[40].

Analysis of the possible pathogenetic factors in our patients with RCN reveals that the renal damage could have resulted either through renal hypoperfusion (blood loss, hypotension) or endothelial injury, either directly (snake envenomation, eclampsia) or through release of various circulating substances (sepsis, pancreatitis). As both mechanisms could lead to endothelin release, it is possible that this acts as the final common messenger producing renal injury leading to RCN. Further studies are needed to establish the exact role of endothelin in the pathogenesis of cortical necrosis.

Conclusion

Renal cortical necrosis is a severe and often irreversible form of Acute kidney injury. The renal prognosis of RCN has improved in recent years in the developing countries, possibly because of wider availability of health care facilities, early detection and treatment of complications in RCN patients and decrease in the incidence of post abortal sepsis due to legalization of abortion law.

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