

## **Dengue associated Acute Kidney Injury in COVID-19 illness**

### **Abstract:-**

Dengue is a viral illness spreads through the bite of Aedes aegypti mosquito leading to a serious health hazard. Dengue induced acute kidney injury is a fatal consequence and there are very few studies reported. Hence early identification of high risk groups is crucial for prevention, to restrict progression and effective treatment of acute kidney injury and to minimise associated morbidity and mortality. The coronavirus disease outbreak has widely spread into a pandemic all over the world. COVID-19 cases have presented with wide spectrum of severity ranging from a mild presentation to severe cases affecting the lungs (ARDS) mainly and rapidly affecting various body organs leading to multiorgan failure. Among these renal involvement is common, the severity of which ranges from mild loss of protein in urine to progressive acute kidney injury requiring renal replacement therapy.

### **Key words:-**

Acute kidney injury, COVID 19, Dengue, Haemodialysis, Renal replacement therapy.

### **Introduction:**

In this case report we are reporting the occurrence of acute kidney injury in a patient who was co-infected with dengue and corona virus.

## **Dengue infection and AKI:-**

Dengue illness is an arthropod transmitted infection prevalent in tropical countries caused by four serotypes (DENV-1, DENV-2, DENV-3, DENV-4), an arbovirus belonging to Flaviviridae family. Human to human transmission occurs by infected female *Aedes aegypti* mosquito bite with an incubation period of three to fourteen days. Wide spectrum of presentation has been reported ranging from self limiting illness to life threatening severe infections such as dengue haemorrhagic fever (DHF), dengue shock syndrome (DSS)[1]

The presentation begins with fever of sudden onset associated with headache, fatigue, myalgia, joint pains and exanthems. Other symptoms include loss of appetite, nausea, vomiting and diarrhea. The classic form of the disease is similar to severe dengue in the early stages, later on followed by haemorrhage, effusions in the cavities, hemodynamic imbalance leading to shock. After three to seven days of disease onset, hemorrhagic manifestations begins which include positive tourniquet test, petechiae, ecchymosis, mucosal bleed and upper GI bleed, thrombocytopenia, hemoconcentration indicative of raised haematocrit and extravasation into cavities (pleural effusion, ascites). The capillary leakage causes plasma loss into peritoneal and pleural cavities leading to hypovolemia which if left untreated progresses to shock. **As the disease severity progresses, patient develops high grade fever, severe pain abdomen, anemia, cold peripheries, restlessness, increased work of breathing, poor peripheral pulses ultimately leading to death.**[2]

The aim of laboratory investigations is to detect the genetic material of dengue virus with the help of various serological or molecular methods out of which ELISA (IgM or IgG) is the most commonly used laboratory test. It detects antibodies against dengue in the blood samples collected during the first six days. In a primary infection, IgM antibodies can be detected in the first four days of symptom onset, peaks by seventh or eighth day, and thereafter the levels

decline and become undetectable after few months. Whereas low levels of IgG antibodies can be detected four days after the symptoms begin with gradually increasing levels and peaks after 14 days and persist for many years.

The molecular test is useful to detect NS1 antigen of dengue virus, a glycoprotein in the infected cell membranes produced in huge quantities at early stage of the disease. This test is useful to detect NS1 Antigen at an early stage of the infection.

Laboratory parameters in dengue include leukopenia and in severe cases, there will be further decline in platelet counts, rising hematocrit levels, deranged coagulation and renal profile, decreased C3 levels, **proteinuria** and hematuria.

Early recognition of warning signs in severe dengue plays a vital role in reducing the mortality. Haemodynamic stability is ensured by regular clinical and laboratory monitoring (blood pressure, packed cell volume, platelet count, urine output, bleeding diathesis and sensorium) and follow up.

Severe cases may lead to renal damage with increase in serum creatinine, proteinuria, electrolyte imbalance, glomerular inflammation, acute kidney injury. Dengue infection cause renal insult due to cytopathic injury by virus, immune complexes, impaired immunity, MODS, hemolysis, rhabdomyolysis, nephrotoxic drugs.

Increased capillary permeability is seen in dengue which is due to excessive release of inflammatory cytokines and activated complement proteins leading to capillary leak and plasma loss which causes renal tubular damage which further leads to decreased renal perfusion and AKI.

**Based on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, AKI can be defined by either a rise in serum creatinine by  $>0.3$  mg/dL, an rise in SCr by  $>1.5$ -times baseline, or decrease in urine volume  $<0.5$  mL/kg/hour for six hours.[3]**

The mainstay of treatment in dengue is fluid therapy and supportive treatment. No specific antiviral drug has been proved to be effective in the treatment of dengue. According to WHO circulatory volume should be maintained by judicious administration of crystalloids and out patients can be managed with oral rehydration therapy.

### **COVID 19 illness and AKI:-**

The pathogenesis of acute kidney injury in COVID-19 illness is multifactorial.

#### Prerenal azotemia:-

Presentation of COVID-19 includes fever, volume losses due to vomiting and diarrhoea, and breathlessness.

#### Acute tubular injury:-

Tubular damage in COVID 19 can be due to ischemia or toxins. Type II alveolar cells are affected by the virus leading to activation of immune system and excessive production of cytokines leading to ischemic-reperfusion injury, inflammatory damage, coagulation defects, endothelial dysfunction and programmed cell death.

#### Cardiorenal syndrome:-

Right ventricular failure due to COVID-19 causes renal congestion leading to AKI. Likewise left ventricular dysfunction causes decreased cardiac output and renal hypoperfusion.

#### Viraemia:-

Virus particles reside in renal endothelial cells suggesting viraemia leading to endothelial damage and AKI. The virus can also infect tubular cells and foot process through an angiotensin converting enzyme 2 (ACE2)-dependent

pathway and cause mitochondrial damage, acute tubular necrosis, collapsing glomerulopathy, and protein leakage in Bowman's capsule.

#### Cytokine storm:-

Immune dysregulation in response to COVID 19 causes excessive release of cytokines leading to cytokine storm.

#### Role of thrombosis in COVID-19 associated acute kidney injury:-

Fibrin deposition occurs in the glomeruli that causes coagulation defects and formation of renal thrombi which further leads to renal dysfunction.

#### Imbalanced RAAS activation:-

Virus binds to ACE2 and causes down-regulation which leads to accumulation of angiotensin II which perpetuates RAAS activation leading to inflammation, fibrosis, vasoconstriction.[4]

AKI is a heterogenous group of clinical disease defined by the impairment of renal function (filtration and excretion) leading to accumulation of nitrogenous wastes and decrease in urine output. AKI can be divided into pre-renal, renal and post renal.

Atypical manifestations of dengue viral infections are encephalitis, intracranial bleed, hepatitis, acalculous cholecystitis, pancreatitis, myocarditis, ARDS.

#### **Case History:-**

A 72 year old male was brought with complaints of multiple episodes of high grade fever with chills, intermittent in nature, generalised body pains, headache, breathlessness of NYHA grade IV, decreased urine output, burning micturition, giddiness. After two days of onset of symptoms patient developed drowsiness, irritability. Patient had no history of cough, chest pain, palpitations, rash, night sweats, weight loss, abdominal pain, vomitings, loose stools, joint pains. Patient

was known case of systemic hypertension since four years on tablet **amlodipine five** mg twice a day. Patient had no history of diabetes mellitus, tuberculosis, bronchial asthma, thyroid disorder. Patient has history of COVID 19 positive status diagnosed one month back with a score of 17/25. On examination patient's general condition was poor, **afebrile** with tachycardia having pulse rate of 116/minute with raised blood pressure 150/100 mm Hg. He was hypoxic with O<sub>2</sub> saturation of 78% on room air, 94% on 15 litre oxygen. Respiratory examination revealed bilateral infra-scapular and infra-axillary crepitations. On central nervous system examination patient was drowsy, irritable, not responding to verbal commands having GCS-E4V3M4, tone normal, power could not be assessed, deep tendon reflexes were normal, bilateral plantar was extensor. Cardiovascular and abdominal system examination were normal. Chest X ray showed bilateral opacities predominantly in right upper, middle and lower lobes and left upper and lower lobes. USG Abdomen and pelvis showed Grade two fatty liver and raised cortical echotexture of kidneys with altered cortico-medullary differentiation with mild splenomegaly. HRCT thorax revealed patchy areas of ground glass opacities in bilateral lung fields predominantly in peripheral subpleural regions, showing CORADS-5 with CT severity score of 9/25 suggestive of viral pneumonitis most likely COVID 19. ECG showed sinus tachycardia. CT Brain was suggestive of focal old ischemic lesions in basal ganglia and corona radiata bilaterally, no haemorrhagic lesions seen.

Blood investigations on admission revealed urine albumin ++, 2-4 pus cells/hpf, serum calcium 8.7 mg/dl, serum magnesium 2.4 mg/dl, serum phosphorous 5.9 mg/dl, serum uric acid 11.1 mg/dl, alkaline phosphatase 172 U/L, SGPT 68 U/L, SGOT 59 U/L, hypoalbuminemia 2.6 g/dl, ABG suggestive of metabolic acidosis, dengue IgM positive.

Patient was started on antibiotics Meropenem, Doxycycline, Clindamycin, intravenous fluids, paracetamol, antihypertensives. Patient underwent 3 sessions of heparin free haemodialysis as patient had thrombocytopenia to avoid risk of haemorrhage.

Table 1. Case history of patient

Date	3/9/21	4/9/21	5/9/21	7/9/21	9/9/21	10/9/21	11/9/21
Urea(mg/dl)	163	156	138	119	94	82	49
Creatinine(mg/dl)	7.7	6.4	5.2	3.8	2.6	1.8	1.1
Sodium(mmol/l)	142	141	140	142	140	140	139
Potassium(mmol/l)	6.4	6.0	5.8	5.0	3.9	3.5	3.7
WBC(cells/cumm)	11300	11200	9400	8100	6100	7600	7200
Platelet(cells/cumm)	66000	75000	1.05 lakh	1.46 lakh	1.55 lakh	1.62 lakh	1.76 lakh
Hb(g/dl)	13.1	12.7	12.9	11.9	11.7	11.8	11.8
HCT(%)	42	45	39	42	39	35	33

During the course of hospital stay, sensorium got improved, breathlessness reduced, urine output increased, O<sub>2</sub> saturation improved, metabolic acidosis improved, platelet counts increased. Hyperkalemia got normalised with serum potassium 3.7 mmol/l, azotemia improved with serum urea 32 mg/dl and serum creatinine came down to 1.1mg/dl.

### **Discussion:**

The main aim in treating dengue associated AKI is restoration of haemodynamic status by fluid therapy using either crystalloid or colloids. Early recognition and prompt treatment helps to decrease mortality and to prevent progression into chronic kidney disease. Early identification of warning signs is important to prevent associated complications. Judicious fluid therapy helps to

prevent volume overload and pulmonary oedema, right ventricular overload, congestion, and subsequent AKI.[5]

The role of intravenous corticosteroids in severe dengue is controversial. Renal replacement therapy may be required in dengue associated AKI however there are no specific recommendations regarding the initiation and frequency.

Renal replacement therapy is indicated in cases of failed conservative management and in patients with volume overload. Disease severity can be curtailed by prompt intervention by renal replacement therapy and extracorporeal organ support.

Dalugama, Gawarammana 2018, Aishah Ali et al 2015, Repizo et al 2014, Sargeant et al 2013, Avasthi et al 2012, Wijesinghe et al 2013, Mehra et al 2012 had conducted studies and proposed various mechanisms of occurrence of AKI in dengue like rhabdomyolysis, acute tubular necrosis, immune complex deposition, Hemolytic uremic syndrome. Majority of these studies have emphasized the role of fluid therapy and hemodialysis as the main modalities of treatment for the treatment of dengue illness.[6]

Fabrizio fabrizi et al had conducted a study to evaluate the frequency of occurrence of AKI and the requirement for dialysis in COVID-19 patients. The study concluded the incidence of AKI in COVID-19 was around 15% whereas the frequency in severe illness was higher around 50%.

Cheng et al had conducted a study to improve awareness of the incidence of renal dysfunction in COVID 19 illness and had found that there is high incidence of hematuria, proteinuria in the enrolled subjects. They had also found increased serum creatinine and BUN levels suggesting renal damage. The study concluded that incidence of AKI in COVID 19 depends on the severity of infection. They had also studied the need for renal replacement therapy in

COVID 19 induced AKI and found that less than 1% of survivors required RRT indicating poor prognosis.

Edouard L Fu et al had studied the incidence of AKI and requirement of renal replacement therapy in COVID 19 induced AKI. The study also showed that age, male sex, cardiovascular disease, diabetes mellitus, hypertension and chronic kidney disease were associated with the occurrence of AKI.[7]

Our patient had presented with altered sensorium, oliguria, fever and breathlessness in a desaturated state on room air. On examination bilateral infraaxillary and infrascapular crackles present, chest X ray suggestive of bilateral heterogenous opacities, so patient was treated with injectable antibiotics and judicious fluid therapy after which patient had gradually improved in saturation and breathlessness. But there is no improvement in sensorium and as patient has metabolic acidosis, hyperkalemia, oliguria and azotemia.

We managed AKI which was the consequence of dengue and COVID-19 illness with renal replacement therapy in the form of heparin free haemodialysis to prevent haemorrhage as patient had thrombocytopenia.

During the course of hospital stay there was improvement in sensorium, breathlessness, urine output, O<sub>2</sub> saturation, metabolic acidosis, platelet count and azotemia.

### **Conclusion:-**

In addition to mortality caused by DAKI, it also leads to increased hospital stay posing a burden to patients and health care system. Hence timely detection of AKI in severe dengue cases plays an important role in prevention of complications. Renal involvement is common in COVID 19 illness and may lead to worst outcomes in severe cases if not intervened at right time. Prompt intervention and initiation of RRT at an appropriate time can alter the clinical

outcome, immediate mortality, and long-term morbidity. Management of AKI is supportive and appropriate measures are to be taken to ensure optimal haemodynamic and volume status, and renal replacement therapy where indicated.

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