Overview of pigmented nephropathy

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Abstract:

Pigment nephropathy defined as an abrupt decrease in renal function due to the toxic effect of endogenous haem-containing pigment on the kidney like myoglobin which released from skeletal muscle in rhabdomyolysis and free hemoglobin in intravascular hemolysis and bile pigment in cholestasis. pigment nephropathy is one of the causes of acute kidney injury labile iron playing a central role in renal sideropathy.

Inflammation is the most important mechanism of pigment induced acute renal injury. Sterile inflammation is mediated through the inflammasome. The most important one is nucleotide-binding domain-like receptor protein 3 (NLRP3) which involved in most inflammatory mediated renal diseases.

Inhibiting the inflammasomes may significantly reduce damaging which occurs in the kidney.

Prevention playing a vital step in the management of pigment nephropathy, clinical suspicion, and biochemical investigations is a challenge to identify the risk of the condition before progression to AKI.

Intravenous fluid replacement to correct hypovolemia and guard against cast formation in the renal tubules preventing progression to acute renal failure.

Keywords: pigment, AKI, rhabdomyolysis.

Definition:

Rapidly decrease in kidney function due to the toxic effect of endogenous haem-containing pigment on the renal tissues[1].

Etiology:

Rhabdomyolysis, intravascular hemolysis and bile pigment nephropathy [2].

Pathogenesis:

Endogenous haem-containing pigment-protein precipitation in renal tissues induce Inflammation through triggering innate immune system which releases inflammatory cytokines and chemokines by endothelial cells and the epithelial cells of the renal tubules resulting in leukocyte recruitment which enhances the progression of kidney injury[3]. Variable studies aimed at demonstrating the mechanisms of kidney injury in haem-pigment nephropathy and the role of inflammasomes in this process [4].

Pigment- containing protein can stimulate and activate (NLRP3) inflammasome[5]Which stimulates the release of pro-inflammatory cytokines and chemokines [6].

The mononuclear phagocytes in the renal tissues expresse the receptors for the NLRP3-ASC assembly and formation and release IL-1β and IL-18[7].

Rhabdomyolysiss induced AKI

Myoglobin present in the muscle tissues which is a pigment containing protein and responsible for binding and delivery of oxygen in the muscle cells for oxidative metabolism. free myoglobin enters into circulation. Myoglobin molecules can cause renal injury by renal vasoconstriction, proximal tubular necrosis, and distal tubular obstruction [8]. In acidic PH myoglobin can be precipitated inside the renal tubules [9]. laboratory diagnosis is done by elevated

serum creatine kinase, urine dipstick positive for blood without RBC in microscopy examination[8]. Serum CPK can be used as a marker for the diagnosis of rhabdomyolysis. [10].

Haemoglobin-Mediated Pigment Nephropathy:

Intravascular hemolysis is one of the most important causes of pigment induced kidney injury. Precipitation of free iron and hemosiderosis in the renal tissues have a deleterious effect on the kidney, [11]. Haptoglobin bind to free hemoglobin which released from red blood cells after hemolysis, the reticuloendothelial cells phagocyte and degrades haptoglobin-hemoglobin complex, free plasma hemoglobin degraded into heme and globin [12]. Heme proteins concentrated and precipitated in the renal tubules which decreased renal perfusion due to increased renal vasoconstriction, renal tubular necrosis and intratubular casts formed in the renal tubules resulting from the bounding of heme proteins with Tamm–Horsfall protein. [13]. Hemolysis triggers inflammatory responses via the NLRP3 inflammasome [14].

Bile pigment induced nephropathy

In marked jaundice patients when the level of serum bilirubin is markedly elevated above 20gm/dl causing nephropathy in which bile pigment and bilirubin have direct toxicity on the renal tubules leading to proximal tubular necrosis and bile cast formation which lead to distal tubular obstruction[15]. The mechanism of acute kidney injury in bile cast nephropathy is analogous to that of renal injury due to myeloma and myoglobin casts. Excretion of high levels of bile acids causes oxidative damage to the tubules. Once excretion is saturated, cast formation and tubular obstruction occur [16].

Management :

Inhibiting NLRP3 inflammasome molecules is recently studied in several experimental and humans researches in the last years, demonstrating the great benefit and effectiveness in a large number of renal diseases in which inflammasome mediated. Both IL-1 inhibitor and MCC950 and β-hydroxybutyrate is a specific inhibiting molecule for NLRP3[17].

NLRP3 Inflammasome Inhibitors:

MCC950 molecule is a new 2nd generation sulfonylurea.it is a diarylsulfonylurea-containing drug specifically inhibiting activation of the NLRP3 [18].

IL-1β and IL-1 Receptor blockers

Canakinumab is a strong monoclonal antibody specific for IL-1β [19,20].

Anakinra is a recombinant human IL-1R blocker, competitive inhibitor with IL-1β for binding with the IL-1R[21].

In hemoglobin induced pigment nephropathy sodium bicarbonate has a beneficial role which changes PH of the urine to alkali preventing cast formation in the renal tubules, decreasing cellular uptake of the proximal tubules to free hemoglobin decreasing its damage and decreasing free iron-mediated free oxygen radical reducing oxidative stress in renal tissues [22].

In hyperbilirubinemia induced kidney injury:

Reducing the blood level of bilirubin early resulting in regression of the deterioration in kidney function. Renal replacement therapy may be needed in severe cases [23].

There are no guidelines or consensus regarding the treatment for bile cast

nephropathy. There are case reports of patients being treated with plasmapheresis for bile cast nephropathy as in multiple myeloma [24].

In rhabdomyolysis-associated AKI:

Prevention is the most important step. Sodium bicarbonate and Intravenous fluids to increase renal blood flow and increase the urinary flow is a very important step for prevention [25]. Start renal replacement therapy, if there is hyperkalemia, hypercalcemia, anuria or hypervolemia [26].

Intermittent hemodialysis or continuous techniques using an EMIC2 dialyzer (cut-off 40kD) is effective in myoglobin removal as myoglobin has a Pm of 17kD and is not removed by high-flux dialyzers [27,28].

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