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REVIEW ARTICLE

A SYSTEMATIC REVIEW ON ACUTE KIDNEY INJURY AMONG CHILDREN WITH SEVERE MALARIA

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Abstract

Malaria is a life-threatening disease caused by Plasmodium species and transmitted by female Anopheles mosquitoes. Acute Kidney Injury (AKI) in children with severe malaria is common and associated with adverse hospital outcome. It has become increasingly prevalent in both developed and developing countries and it is associated with severe morbidity and mortality especially in children. The recognized factors associated with acute kidney injury among children with severe malaria are sociodemographic factors (age, sex, age of parents and level of education of parents); clinical factors and laboratory factors such hyperparasitaemia, hypoglycaemia, low level of haemoglobin and thrombocytopenia. This review showed that there is a high prevalence of acute kidney injury among children with severe malaria. Acute kidney injury among children with severe malaria is associated with low level of education of caretakers, young age of children, history of receiving NSAIDs and anaemia. The mortality rate of children with AKI is high.

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Introduction:-

Malaria is a life-threatening disease caused by Plasmodium species and transmitted by female Anopheles mosquitoes (WHO, 2019). In history malaria was taken as a zoonotic disease in the primates of Africa through the 21st century. Malaria is a life threatening human infectious disease, worlwide except Antarctica and the most important factors in the spread or eradication of disease have been human behaviour and living standards(Obeagu et al., 2014 ; Obeagu, 2016 ; Obeagu et al., 2016). Traditional herbal remedies have been used to treat malaria for thousand years and the bark of cinchona tree which contains quinine have been the first effective treatment for malaria (Benelli and Beier, 2017).

In Europe malaria was introduced from the southeast during the Neolithic period and spread throughout the continent due to a favourable climate; until the end of Second World War malaria was endemic in Europe (Evangelia, 2018). In 1955 the eighth world health assembly agreed that the World Health Organization (WHO) should initiate the program of eradication and in 2015 for the first time the WHO European region reported zero indigenous malaria cases (WHO, 2016). In the United States, the history of malaria started way back in 15th century until today where it still affects local residents (Brown, Solomon, Lerner & Del Rio., 2020). Malaria originated from fossil mosquito and the first case of disease in America is believed to be after the arrival of explorer Christopher Columbus in 1492.

Prevalence of AKI among children with severe malaria

Acute Kidney Injury (AKI) in children with severe malaria is common and associated with adverse hospital outcome. It has become increasingly prevalent in both developed and developing countries and it is associated with severe morbidity and mortality especially in children (Cerda et al., 2008; Obeagu et al., 2017 ; Ogbonna et al., 2021 ; Nwosu et al., 2016). Prasad and Mishra (2016) published a study in India whose aim was to observe the renal involvement, associated morbidities and outcome found that among 159 children, 31 (19.9%) were diagnosed with AKI based on PRIFLE (Paediatric Risk Injury Failure Loss and End-stage kidney disease) classification. In Brazil, Lana et al. (2017) published a research which showed that malaria was the first parasitic infection to be clearly associated with glomerular diseases. They found that severe malaria can cause disease in glomerular and interstitial region.

In sub-Sahara Africa different studies have been conducted and showed the burden of AKI among children with severe malaria. Oshomah (2019) in Nigeria published a cross sectional study whose aim was to determine the prevalence and predictors of AKI among children with severe malaria found that among 245 children with severe malaria 94 (38%) had AKI. In Togo, Sabi et al. (2018) conducted a retrospective study which aimed to describe the clinical, biological and evolutionary profile of AKI due to severe malaria in Togolese children and found that out of 338 children 24 (7,1%) were diagnosed with AKI based on pPRIFLE criteria. Kunuanunua et al. (2013) during their prospective cohort study with the aim to determine the prevalence of acute renal failure among children with severe malaria in Kinshasa Democratic Republic of Congo found a prevalence of 23.6%.

Factors associated with AKI among children with severe malaria

The recognized factors associated with acute kidney injury among children with severe malaria are sociodemographic factors (age, sex, age of parents and level of education of parents); clinical factors and laboratory factors such hyperparasitaemia, hypoglycaemia, low level of haemoglobin and thrombocytopenia (Zaki et al., 2013).

Sociodemographic factors

Previous studies showed increased prevalence of AKI among children with severe malaria. In Nigeria, Oshomah (2019) found that male sex was more prevalent among children with AKI and represented 53.3% of the study participants and the median age was 3.5 years. A prospective study conducted by Kunuanunua (2013) in Kinshasa (DRC) showed that among 378 children with AKI associated to severe malaria, 226 were boys (59.8%) and 152 were girls (40.2%). During their study, Chami et al. (2019) in Tanzania found that among 513 children with severe malaria, 297 were male (57.9%) and 216 (43.1%) were female. For Akobye (2014) in Mulago Hospital, there was no significant association between the sociodemographic factors (sex and age) with AKI among children with severe malaria; the age above 5 years, the male sex were not significantly associated with AKI among children with severe malaria (respectively p value of 0.673; 0.245; 0.382; 0.501).

Medical factors associated with AKI among children with severe malaria

Clinical presentation

Malaria is a life-threatening disease caused by Plasmodium species and transmitted by female anopheles mosquitoes and can have various clinical features (WHO, 2019). Malaria is one of the causes of AKI in rural and urban setting and can be prevented by intervention at the individual community and regional level (Cerda et al., 2008). Zaki et al. (2013) in India conducted a retrospective study, which aimed to evaluate the incidence, clinical features, course, outcomes and predictors of mortality of AKI in children with malaria. They found that 100% of children with AKI and severe malaria were vomiting, 75% of them had oliguria, 41.7% had cerebral malaria, 66.7% had anaemia, 83.3% of them developed haemolysis, 66.7% were in circulatory collapse and 41.7% developed hyperbilirubinaemia.

The retrospective study conducted by Okpere et al. (2017) in Nigeria among 960 children with severe malaria whose aim to determine the prevalence of AKI in children with severe malaria found that 80% of them had oliguria and 59.4% had proteinuria. Another cross-sectional study conducted in Nigeria by Oshomah in 2019, showed that children with severe AKI had oliguria (22.4%), jaundice and impaired level of conscious. They also found that AKI among children with severe malaria was associated with metabolic acidosis. Sabi et al. (2018) in their retrospective study which aimed to describe clinical, biological and evolutionary profile of AKI due to severe malaria in Togolese children found that 87.5% presented with haemoglobinuria, 79.2% had severe anaemia and 75% had fever. Kunuanunua (2013) found in his study conducted in Kinshasa (DRC) that among 378 children with severe malaria 87 had black water fever.

Chami et al. (2019) in their study in Tanzania found that haematuria, fever, dysuria, rash, diarrhoea, vomiting were present among children with malaria and AKI but they were not statistically significant. AKI among children with severe malaria was associated with the presence of sore throat, skin infection (P=0.024), sickle cell (P=0.006) and dehydration (P=0.001). Akobye (2014) during her cohort study in Mulago Hospital (Uganda) found that AKI was seen in all children with cerebral malaria, and shock. She found also that haemolysis, severe anaemia and dehydration were not associated with the occurrence of AKI. Still in Uganda, Conroy et al. (2016) found during their prospective study in Jinja (Uganda) that fever, tachycardia and impaired level of consciousness were significantly associated with AKI (p-values: 0.014, 0.011 and 0.033). They also found that vomiting, tea coloured urine were significantly associated with AKI among children with severe malaria (p-values: 0.002 and 0.025) and AKI among children with severe malaria was associated with the presence of severe retinopathy ($p < 0.05$). They found also that severe anaemia was not significantly associated with AKI among children with severe malaria (P value of 0.382).

Duration of illness

In India Prasad and Mishra (2016) found that the duration of illness among children with severe malaria who developed AKI was 7.5 ± 2.07 compared to 5.6 ± 1.1 of those without AKI and the longer duration of illness and late presentation at the hospital complicated the course of the disease. In Uganda, Akobye (2014) found that the duration of illness of one week or more was not significantly associated with AKI among children with severe malaria.

Previous medication among children with AKI in severe malaria

Sabi et al. (2018) in their retrospective study which aimed to describe clinical, biological and evolutionary profile of AKI due to severe malaria in Togolese children found that children with AKI and severe malaria were on the following medication before hospitalization: quininine (25%), artemether (8.33%), analgesic (20.83%), anticonvulsant (8.33%) and traditional medication (4.17%). In Tanzania, Chami et al. (2019) found previous use of herbal medicine was significantly associated with AKI among children with severe malaria (p= 0.007). They also found that 8.4% of children with AKI and severe malaria were on gentamycin, 9.6% of them were on ceftriaxone and 12.1% on non-steroids anti-inflammatory drugs (NSAIDs). In Uganda, Conroy et al. (2019) found that children with severe malaria who developed AKI were on NSAIDs (5.5%), gentamycin (1.8%) and any other nephrotoxic medication (7.3%). This study was conducted in a rural setting and a region with a hot temperature where the risk of dehydration is high therefore increase the occurrence of AKI which can be worsened by severe malaria.

Diagnosis of AKI and laboratory features associated with AKI among children with severe malaria

Diagnosis of AKI among children with severe malaria

A standardized definition of AKI was proposed by the Kidney Disease Improving Global Outcomes (KDIGO) AKI working group in 2012 and has been validated in pediatric populations subsequently (Heung et al., 2016). It is recommended that the KDIGO AKI definition and staging be used to guide clinical care, and outcome measure in AKI pediatric studies. This definition identifies and stages of AKI based on changes in serum creatinine from baseline or urine output in 3 stages as follows: stage 1 is characterized by increased in serum creatinine (Scr) by 1.5 to 1.9 time baseline or urine output less than 0.5ml/kg/h for 6- 12h; Stage 2 by an increased Scr 2 – 2.9 times baseline or urine output less than 0.5ml/kg/h for more than or equal to12h and stage 3 by an increased Scr > 3 times baseline, or urine output < 0.3ml/kg/h for more than or equal to 24h or anuria for more than 12h , or GFR< 35ml/min/1.73m^3 (Ciccia and Dvarajan., 2017). In previously healthy children where the baseline serum creatinine is unknown, it is generally recommended to use a presumed baseline of 120 mL/min/1.73 m^2. An alternative approach is to use published minimum and maximum normative serum creatinine values for age and gender (De Rosa, 2016)

Prasad et al. (2016) in India, used pRIFLE criteria for the diagnosis of AKI in their study. The same way Sabi et al. (2018) in their retrospective descriptive study in Togo they used modified RIFLE criteria for pediatric for the diagnosis of AKI. Akobye (2014) conducted a cohort study in Mulago and made the diagnosis of AKI using pRIFLE criteria. However, Oshomah et al. (2019) used KDIGO definition of AKI in their cross sectional study by measuring the Scr on admission and after 24h, the creatinine on admission was used as baseline and Conroy et al. (2019) in their prospective cohort study used also the KDIGO criteria for defining AKI and it was done based on single creatinine level with baseline creatinine estimated using community children's creatinine. Shami et al. (2019) did a cross sectional study where eGFR was calculated using modified Schwartz equation and those < 60ml/min/1.73m^3 were consider to have renal dysfunction.

Laboratory features associated with AKI among children with severe malaria

Zaki et al. (2013) in their study with the aim to analyze the clinical features, course, outcome, and predictors of mortality in children having acute renal failure following malaria in India found that hyperparasitaemia was significantly associated with AKI among children with severe malaria with a P-value of 0.0046. In the same note Prasad and Mishra (2016) in their study found that parasite density of above 3 plus (+++) was found to be significant factor associated with mortality among children with AKI and severe malaria. Chami et al. (2019) in Tanzania found that AKI among children with severe malaria was associated with proteinuria (P<0.001). In their prospective study in Jinja, Conroy et al. (2016) found that AKI among children with severe malaria was associated with azotaemia and a high level of lactate (P value <0.05, they found also that haemoglobinuria was not significantly associated with AKI among children with severe malaria (P value of 0.382). Still in Uganda,Akobye (2014) in Mulago Hospital found also that haemoglobinuria was not associated with the occurrence of AKI.

Severity of AKI among children with severe malaria

The evolution in the definition of AKI began in 2004 when the acute dialysis quality initiative proposed RIFLE criteria which included three stages of AKI: risk, injury, failure and two outcomes loss and end stage kidney disease. In 2007 a pediatric version of RIFLE the pediatric pRIFLE was developed and validated. The KDIGO definition represent the most recent consensus definition which is currently recommended for use in pediatric most recent for clinical and research purpose (Heung et al., 2016). In India, Zaki et al. (2013) found during their study that dialysis was initiated in only one patient and all the three patients who expired had multiorgan dysfunction, and death occurred within 48 hours of admission. Another study conducted in India by Prasad and Mishra (2016) found that among 31 children with AKI 4 (12.9%) were classified at risk, 11 (35.4%) at injury and 16 (51.6%) at failure by using pRIFLE criteria.

In Togo, the research conducted by Sabi et al. (2018) showed that AKI was diagnosed in 24 children among 338 children admitted with severe malaria, a prevalence of 7.1% and they were classified according to pRIFLE where 10 (3%) children fulfilled risk, 9 (2.6%) children fulfilled injury and 5 (1.5%) children fulfilled failure.

Akobye (2014) found in Uganda during her study using pRIFLE criteria that 74% of children fulfilled pRIFLE risk, 14% of children fulfilled injury and 12% pRIFLE fulfilled failure. She found also the mortality rate was 33.0% among those who fulfilled failure; 14.6% among those who fulfilled injury and 2.6% among those who fulfilled risk. Another study conducted in Uganda by Conroy et al. (2016) in Jinja found that among 81 children who have KDIGO definition, 42 (51.9%) were in stage I and among them 5 (11.9%) died; 18 (22.2) were in stage II and among them 3 died (11.1%); 21 (25.9%) were in stage III and among them 4 (23.8%) died.

Outcomes of children with severe malaria and AKI

Duration of hospitalization

Oshomah et al. (2020) conducted a cross-sectional study whose aim was to determine the prevalence of AKI in children with severe malaria and its association with adverse hospital outcomes in Nigeria, found that children classified in stage 3 spent nine days in hospital compared with eight days, six days and six days spent in the hospital by children with stage 2, 1 and no AKI, respectively (p< 0.001). In Uganda, Conroy et al. (2016) in Jinja found that the duration of hospitalization increased across stage of AKI. They found that the duration of hospitalization among children with severe malaria was significantly associated with AKI (p=0.002). They found that the duration of hospitalization was of 62 hours, 78 hours, 80 hours and 103 hours respectively for children without AKI, children in stage I AKI, children in stage II AKI and in stage III AKI.

Survival among children with severe malaria and AKI

During his retrospective study India, Zaki et al. (2013) found that the mortality rate among children with AKI secondary to severe malaria was 25% (p=0.004) and 75% of children recovered. He also found that cerebral malaria, hyperbilirubinemia and Disseminated Intravascular Coagulation (DIC) were associated with poor prognosis for morbidity and AKI mortality. Another study conducted in India by Prasad and Mishra (2016) showed that 25.8% of children with AKI and severe malaria died, those who died were having increased blood urea nitrogen and oliguria. They also found that the following factors were significantly contributing to mortality: DIC, jaundice, hyperparasitaemia and pulmonary edema.

In Nigeria, Oshomah et al. (2020) during their cross-sectional study found that the mortality was increased in both children who were having oliguria and increased serum creatinine than those increased serum creatinine only (50%

versus 4.8%, p < 0.0011); loss of conscious and jaundice were associated with increased odd dying. In Uganda, Akobye (2014) in her study found that the mortality rate among children with AKI who were classified as failure was 33%, those classified as injury were having a mortality rate of 14.3% and those classified as risk were having a mortality rate of 2.6%. Conroy et al. (2016) in Jinja (Uganda) got a mortality rate of 14.8% and during their study of 2019 in Mulago Hospital they found that the intra-hospital mortality was 11.9% among children with AKI in severe malaria compared to 4.2% among those without AKI in severe malaria. However, the post discharge mortality was of 4.7% among children with AKI in severe malaria compared to 1.3% among those without AKI.

Conclusions:-

This review showed that there is a high prevalence of acute kidney injury among children with severe malaria. Acute kidney injury among children with severe malaria is associated with low level of education of caretakers, young age of children, history of receiving NSAIDs and anaemia. The mortality rate of children with AKI is high.

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