Scientific Research Publishing

Open Journal of Nephrology, 2018, 8, 10-17
http://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

Prognosis of Acute Renal Failure of the Child during Severe Malaria in Niamey-Niger

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How to cite this paper: Tondi, Z.M.M., Garba, M., Abderraman, G.M., Moussa, H.D., Hamat, I., Toure, E.S., Abdou, I., Toure, I.S., Illiassou, A. and Niourou, S. (2018) Prognosis of Acute Renal Failure of the Child during Severe Malaria in Niamey-Niger. *Open Journal of Nephrology*, **8**, 10-17.
https://doi.org/10.4236/ojneph.2018.81002

Received: November 28, 2017
Accepted: March 4, 2018
Published: March 7, 2018

Abstract

Introduction: In malaria-endemic areas, acute renal failure (ARF) is one of the most serious complications, it occurs in 40% of severe forms of malaria in adults and is linked to 75% of deaths, especially when extra-renal cleaning is not available. In children, studies of ARF during malaria are limited. We have no published studies on this topic in Niger. The main objective of our study is to evaluate the prognosis of ARF during severe malaria in children. **Patients and Method:** This is a one-year prospective study (January 1, 2016 to December 31, 2016) conducted in the resuscitation unit of the pediatric department of the National Lamordé Hospital of Niamey (Niger). We included in the study children aged 0 to 15 years hospitalized for severe malaria with impaired renal function. Patients who had chronic renal failure or who had acute renal failure with a thick negative drop were excluded from the study. Acute renal failure is defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria basing on creatinine clearance. **Results:** The incidence of ARF was 12.60%. The mean age of the patients was 4.25 ± 1.3 years [8 months - 15 years]. The mean hemoglobin level was 8.2 ± 2.7 g/dl. In 54.02% of cases, the hemoglobin level is ≤5 g/dl. Mean serum creatinine was 543.7 ± 69.5 µmol/l [107 - 2500 µmol/l] and mean azotemia was 27.5 ± 3.5 mmol/l. Severe anemia (54.02%) were more related to the occurrence of ARF(with p = 0.014). According to the RIFLE classification, 55 patients (63.22%) were in the Risk stage, 18 patients (20.69%) were in the injury stage and 14 patients (16.09%) in the failure stage. All patients were placed on injectable Artesunate. The average length of hospital stay was 8.6 ± 4.5 days [5 to 22 days]. Dialysis was reported in 15/87 (17.24%). For technical and financial

reasons only 8 patients were hemodialysed. Indications for dialysis were severe uremic syndrome 7 cases (8.04%), fluid overload 5 cases (5.75%) and severe hyperkalemia 3 cases (3.45%). **Conclusion:** The etiological factors of ARI in malaria were massive hemoglobinuria, severe anemia and shock. Adequate management of simple cases of malaria and the early transfer of severe cases to resuscitation services can prevent certain complications such as acute renal failure.

Keywords

Acute Renal Injury, Malaria, Niger

1. Introduction

Malaria is the most common parasitic disease in the world. It represents a major public health problem, especially in tropical and subtropical countries [1]. About 500 million people worldwide have malaria each year. It is responsible for 1 to 3 million deaths a year [1]. Children and women pay the highest price for the disease. More than two-thirds (70%) of deaths from malaria occur in the under-5 age group. Severe forms are the most lethal of the disease [1] [2]. Acute renal failure is one of the most serious complications. In malaria-endemic areas, acute renal failure (ARF) occurs in 40% of severe forms of malaria in adults and is linked to 75% of deaths, especially when extra-renal cleansing is not available [3]. In children, studies of ARF during malaria are limited. In an Indian study [4], the incidence of ARF during malaria ranged from 13% to 17.8%. In a Congolese series [5], the incidence of ARI in severe forms of malaria was 23.06% with an intra-hospital mortality of 12.6%. In Niger, according to the estimates of the national malaria control program, 770,000 cases were recorded in 2015. It is responsible for 50% of deaths in children under 5 years of age [6]. We have no published studies on ARI and severe childhood malaria in Niger. The main objective of our study is to evaluate the prognosis of ARI during severe malaria in children.

2. Patients and Methods

This is a one-year prospective study (January 1, 2016 to December 31, 2016) conducted in the resuscitation unit of the pediatric department of the National Lamordé Hospital (NLH) in Niamey. The unit has about twenty beds. It serves to stabilize patients in life-threatening situations prior to hospitalization in the pediatric ward. The NLH serves the populations of the right bank of the capital Niamey. It is a region where malaria transmission is endemic with a peak of infestation during wintering (July, August and September). We included in the study children aged 0 to 15 years hospitalized for severe malaria with impaired renal function. Patients who had chronic renal failure or who had acute renal failure with a thick negative drop were excluded from the study. Acute renal

failure is defined according to criteria of Kidney Disease Improving Global Outcomes (KDIGO) basing on clearance of creatinine [7]. The glomerular filtration rate was estimated by the Schwartz formula: Creatinine clearance (ml/min per 1.73 m^2) = [Size (cm) × k]/Cr (mg/dl), k = 0.413 (constant for children aged 1 to 13). Renal impairment is defined as a serum creatinine elevation ≥ 0.3 mg/dl (26 µmol/l) within 48 hours or an increase in serum creatinine ≥ 1.5 times the normal reference value. ARI stage 1 corresponds to serum creatinine ≥26 µmol/l within 48 hours or serum creatine elevation 1.5 to 1.9 times normal; stage 2 = creatine ≥ 2 to 2.9 times normal; stage 3 = creatine ≥ 3 times normal or creatine serum ≥ 4 mg/dl (354 µmol/l). Severe forms of malaria have been defined according to the WHO Malaria Severity Criteria 2012 [1]. The severe forms of malaria are: severe neurological form (severe malaria neurological form) which is defined by at least one seizure within 24 hours, impaired consciousness or coma with a score of Blantyre ≤ 2 in infants or a Glasgow ≤ 11 in older children with normal lumbar puncture; acute pulmonary edema or acute respiratory distress syndrome; the shock state with cold end; macroscopic hemoglobinuria; hemorrhagic syndrome; jaundice associated with organ dysfunction; hypoglycemia (blood glucose < 2.2 mmol/L or < 40 mg/dl); severe anemic malaria (hemoglobin level < 5 g/dl or hematocrit < 15%); metabolic acidosis (bicarbonate < 8 mmol/l or blood pH < 7.35); hyperparasitaemia (more than 5% or 250,000 parasitized red blood cells/µl); acute renal failure (serum creatinine ≥ 265 µmol/l). The diagnosis of malaria was made by a rapid diagnostic test (RDT) positive and confirmed by a thick drop on capillary positive blood. For each patient, sociodemographic characteristics, clinical signs at admission, paraclinical assessment, management elements and prognosis are collected. The data was processed using the SPSS 20.0 software. Descriptive statistics were used to calculate frequencies, averages and standard deviations. We used the chi^2 test in univariate analyzes. A value $p < 0.05$ is considered statistically significant.

3. Results

Six hundred and seventy (690) cases of severe malaria were hospitalized in the intensive care unit during the study period. Of these, 87 had an ARI. The incidence of ARI was 12.60%. The mean age of the patients was 4.25 ± 1.3 years with extremes of 8 months to 15 years. More than the majority (54.02) of patients with ARI were male. They were 49/87 (56.32%) older than 5 years old. 72.41% of patients lived in peri-urban areas. The mean duration of progression of the malaria episode before hospitalization was 8.7 ± 3.03 days. **Table 1** summarizes the clinical signs at admission. Fever (97.70%), vomiting (81.60%) and oligo-anuria (77.01%) were the most prominent clinical signs. The mean hemoglobin level was 8.2 ± 2.7 g/dl. In 54.02% of cases, the hemoglobin level is ≤ 5 g/dl. Mean serum creatinine was 543.7 ± 69.5 µmol/l with [107 - 2500 µmol/l] and mean azotemia was 27.5 ± 3.5 mmol/l. The probable etiological factors of ARI were summarized in **Table 2**. Massive hemoglobinuria (44.83%) with p = 0.001; oliguria (74.71%) with p = 0.021; severe anemia (54.02%) with p = 0.014 were more

Table 1. Clinical signs of patients with ARF at admission.

Signs	Number	Percentage
Fever	85	97.70%
Thrill	45	51.72%
Headache	37	42.52%
Vomiting	71	81.60%
Diarrhea	40	45.98%
Convulsions	41	47.12%
Abdominal pain	13	14.94%
Icterus	52	59.77%
Arthralgia	43	49.42%
Oligo-anuria	67	77.01%
Respiratory distress	15	17.24%
Severe dehydration	36	41.37%
"Coca-cola" Urine	41	47.12%
Disorder of consciousness	36	41.38%

Table 2. Characteristics of patients according to acute kidney failure.

Characteristics	Without ARF (n = 603)	With ARF (n = 87)	P-value
Demographic			
Male	348 (57.71%)	47 (54.02%)	0.065
Female	342 (42.29%)	40 (45.98%)	0.085
Age ≤ 5 ans	404 (67%)	38 (43.68%)	0.253
Age > 5 ans	199 (43%)	49 (56.32%)	0.021
Around urbna	417 (69.15%)	63 (72.41%)	0.001
Urban	186 (30.85%)	24 (27.59)	0.985
Clinic			
Duration of evolution (days)	6.7 ± 2.5	8.7 ± 3.03	0.003
Temperature (˚C)	38.1 ± 0.79	38.3 ± 1.01	0.740
Disorder of consciousness and convulsion	193 (32%)	40 (45.98%)	0.065
Respiratory distress	86 (14.26%)	19 (21.84%)	0.875
Massive hemoglobinuria	54 (8.95%)	39 (44.83%)	0.0001
Hemorrhagic syndrome	21 (3.48%)	12 (13.79%)	0.325
Frankish jaundice	184 (30.51%)	41 (47.12%)	0.002
State of shock	98 (16.25%)	23 (26.43%)	0.074
Oliguria	189 (31.34%)	65 (74.71%)	0.021
Severe anemia	215 (35.65%)	47 (54.02%)	0.014
Paraclinic			
Hyperparasitemia	213 (35.32%)	17 (19.54%)	0.825
White blood cells (10^3/ml)	12.5 ± 2.75	14.870 ± 36	0.745
Hemoglobin (g/dl)	9.9 ± 4.5	8.2 ± 2.7	0.321
Platelets (10^3/ml)	255 ± 25	125 ± 35	0.062
Azotemia (mmol/l)	5.7 ± 3.2	27.5 ± 3.5	0.001
Serum Creatinin (µmol/l)	11.2 ± 5.2	543.7 ± 69.5	0.012
Natremia (mmol/l)	137 ± 25	139 ± 14	0.925
Kaliemia (mmol/l)	4.7 ± 1.5	4.9 ± 2.8	0.065

related to the occurrence of ARI. According to the RIFLE classification, 55 patients (63.22%) were in the Risk stage, 18 patients (20.69%) were in the injury stage and 14 patients (16.09%) in the failure stage (Table 3). All patients were placed on injectable Artesunate combined with adjuvant treatment according to the clinical presentation of the patient. Those with severe anemia were transfused with red blood cells or whole blood. The primary management of ARI was overhydration and/or forced diuresis using intravenous furosemide at a dose of 6 mg/kg/day to be divided into 3 doses. The average length of hospital stay was 8.6 ± 4.5 days with extremes of 5 to 22 days. Dialysis was reported in 15/87 (17.24%). For technical and financial reasons, only 8 patients were hemodialysed. Indications for dialysis were severe uremic syndrome in 7 cases (8.04%), fluid overload in 5 cases (5.75%) and severe hyperkalemia in 3 cases (3.45%). Complete recovery of renal function was noted in 63 patients (74%). Partial recovery of renal function was observed in 8 patients (7%) and a change to chronic renal failure in 3 patients. Thirteen patients died during hospitalization. Six on thirteen patients (6/13) of the deceased patients were at stage 3 of acute renal failure. Severe anemia ($p = 0.001$), massive hemoglobinuria ($p = 0.002$) and severe malaria neurological form ($p = 0.032$) were more associated with mortality.

4. Discussion

Acute renal failure is one of the serious complications of malaria. Our study showed that ARI in severe childhood malaria was more common in males, the majority of patients were older than 5 years. Hemoglobinuria and anemic forms were more associated with the occurrence of ARI. Patient's mortality in our study, was 14.94%. This mortality is greater during severe malaria neurological form and massive hemoglobinuria and severe malaria neurological form. The incidence of ARI due to malaria in adults in some series was around 6% [8] [9].

Table 3. Prognostic factors of severe malaria and ARF.

Factors	Survived N = 74	Death N =13	P-value
Hyperparasitaemia	25	5	0.062
Severe Anemia	32	8	0.001
Massive hemoglobinuria	14	7	0.002
Hemorrhagic syndrome	3	4	0.325
Neurological malaria	42	9	0.032
Oligo-anuria	37	12	0.0001
State of shock	6	4	0.124
Frankish jaundice	29	6	0.065
Respiratory distress	8	3	0.085
RIFLE Classification			
RISK	52	3	0.985
INJURY	14	4	0.074
FAILURE	8	6	0.05

Recent studies in children have reported an incidence ranging from 0.6% to 48.6% [10] [11] and [12]. During our study, it was 12.60%. The incidence of ARI would be influenced by certain parameters such as sample size, time to admission, degree of malaria infection and admission status of patients [10]. Several factors are involved in the mechanism of occurrence of ARI during malaria. Massive intravascular hemolysis causing hemoglobinuria; cytoadherence and erythrocyte sequestration with intravascular coagulation, responsible for hypo-infusion; dehydration and hypovolemia secondary to fever, profuse sweating, lack of water intake and digestive disorders also leading to renal hypoperfusion; activation of monocytes with release of cytokines, free radicals and immunoglobulins [13] [14]. All these phenomena lead to a tubular and cortical necrosis. Among the risk factors for the occurrence of ARI in our study is the massive hemoglobinuria. In a series reported by kavitha *et al.* [15], the important risk factors for the occurrence of ARI during malaria were jaundice, hepatomegaly, low diastolic pressure, hyperbilirubinemia. Several studies of the pediatric population [15] [16] and adults reported a higher prevalence (59.78% to 81%) of ARI in males. In our study more than 54% of the patients were male. Some authors support a significant exposure of men to mosquito bites. But in the pediatric population the risk of exposure being the same, additional studies must be conducted to understand the phenomenon. The oligoanuric form of ARI (77%) is the most important in our study. Several pediatric studies [10] [17] reported similar results. It is more related to hypovolemia due to vomiting and diarrhea that are common in children. Dialysis was indicated in 15 patients but only 8 had benefit from it. The absence of peritoneal dialysis, the very high cost of the procedure and the altered state of some patients were the limiting factors in its implementation. Other African studies [18] [19] have reported similar findings. Despite the limitation of our means of care, 74% of the survivors had completely recovered their renal function and 7% partially. Kapil *et al.* [10] in India reported similar results. In our study, the mortality was 14.94%. It was similar to that reported in the sub region. Other series have reported much higher mortality ranging from 33.3% to 46.2% [20]. The risk factors for mortality in our study were severe anemia, neurological form, and massive hemoglobinuria. For Kapil *et al.* [10], the risk factors for death were oliguria, shock, disseminated intravascular coagulation, central nervous system involvement and respiratory distress syndrome. The occurrence of all these signs summarizes a multi-visceral dysfunction [21]. The limitations of our study are the relatively small size of our sample, the lack of daily monitoring of certain parameters such as diuresis, creatinine and the absence of certain technical means such as peritoneal dialysis. Despite this, we believe that it has brought the light to better understand the incidence, etiological factors and prognosis of ARI during childhood malaria.

5. Conclusion

In our study, the incidence of ARI during malaria was 12.60%. For the male

gender, children over the age of 5 were more exposed to the ARI. The etiological factors were massive hemoglobinuria, severe anemia and shock. Patient's mortality in our study was 14.94%. The risk factors for death were hemoglobinuria, severe malaria, anemic and neurological form. Adequate management of simple cases of malaria and the early transfer of severe cases to resuscitation services can prevent certain complications such as acute renal failure.

Interest Conflict

The authors do not declare any conflict of interest.

Ethics Committee

The preliminary agreement has been obtained.

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Abbreviations

ARF acute renal failure;

ARI: acute renal injury;

NLH: National Lamordé Hospital;

RIFLE: “risk”, “injury”, “failure”, “lost” and “end stage”.