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Acute Renal Failure Related to Malaria in Admitted Patients in Pediatric Hospitals from Dakar, Senegal: A Series of Eleven Cases

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Authors' contributions

This work was carried out in collaboration among all authors. This study was conducted in accordance with the Declaration of Helsinki. To respect the confidentiality, an identification code was assigned to each patient (NK + number). This study was a hospital-based research conducted in routine conditions. All authors read and approved the final manuscript.

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Short Communication

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ABSTRACT

Aims: To firstly determine the incidence of acute renal failure (ARF) related to malaria in a series of 11 cases among admitted patients at the pediatric hospitals in Dakar, Senegal and to lastly measure the performance of rapid diagnostic test (RDT) and microscopy in malaria diagnosis using polymerase chain reaction (PCR) as a gold standard.
Study Design: A bi-centric and descriptive study was carried out.
Place and Duration of Study: From June 2018 to January 2019 in two university hospitals of Dakar, Senegal: Aristide Le Dantec university hospital and Albert Royer university hospital.

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Methodology: Pediatric patients aged under 18 years with confirmed malaria by RDT or microscopy and ARF defined by anuria or oligo-anuria and a decrease in glomerular filtration rate were included. Nested PCR was performed to confirm malaria diagnosis and *Plasmodium* species typing.

Results: In total, 11 ARF cases (8.5%) related to malaria among 130 children infected with malaria parasites were included out of 4,474 hospitalized. Affected children were aged between 2 and 16 years with a mean age of 11 years and a sex ratio of 0.57. For malaria diagnosis, RDTs were positive for all patients while microscopy only revealed 6 cases (54.5%) as well as PCR. However, microscopy and PCR presented two discrepancies. Considering PCR as the gold standard tool, RDT showed a relative high sensitivity (100%) and zero specificity with a positive predictive value (PPV) of 54.6% while microscopy respectively showed a sensitivity and a specificity of 66.7 and 60%.

Conclusion: This study showed the relatedness between ARF and *P. falciparum* malaria. Even though microscopy remains the gold standard for the diagnosis of malaria but microscopists must be regularly trained. In addition, RDT should always be confirmed by microscopy and preferably by PCR.

Keywords: Acute renal failure; malaria; Plasmodium falciparum; children; RDT; microscopy; PCR; Senegal.

1. INTRODUCTION

According to the last malaria report, an estimated 228 million cases of malaria occurred worldwide in 2018. Most malaria cases (93%) were in the WHO African region with *Plasmodium falciparum* as the most prevalent malaria parasite accounting for 99.7%. Children aged under 5 years are the most vulnerable group affected by malaria accounting for 67% of all malaria deaths worldwide [1]. Since 2010, WHO recommended either rapid diagnostic test (RDT) or microscopy confirmation of suspected malaria cases before treatment [2]. However, in many peripheral health facilities of endemic countries, microscopy is not available due to lack of trained microscopists on staff at all times. Likewise, both false-positive and false-negative results have been reported with RDTs worldwide [2,3]. Thus, polymerase chain reaction (PCR) for malaria remains the gold standard for diagnostic confirmation and species identification, with the highest sensitivity and specificity [3]. However, in our context of lack of such testing in our routine, the diagnosis is based on RDT before confirmation by the microscopic detection on peripheral blood sample of erythrocytic forms of *Plasmodium* by thick and thin blood films examination with a result obtained within a maximum of 2 hours [4,5].

Acute renal failure (ARF) is a complication that is one of the major criteria for the severity of *P. falciparum* malaria [6]. Accurate mechanism of ARF in malaria is not clearly known with numerous proposed hypothesis [7]. The mechanism of this ARF associated with malaria seems to be an acute tubular necrosis related to hemoglobinuria [6]. Indeed, malaria may present various clinical forms ranging from simple to severe forms in children and some of these severe forms are accompanied by significant hemolysis and are the basis of many complications including kidney failure [8].

In low and middle-income countries (LMIC), ARF is a challenging problem particularly in Africa where it is estimated that 150 million patients develop ARF per year, mainly caused by infectious diseases such as malaria. The incidence of ARF related to *P. falciparum* has increased in LMIC [9]. In Senegal, this incidence is unknown or is underestimated notably in children who represent a vulnerable group for malaria. Therefore, this study aimed to firstly determine the incidence ARF related to malaria in a series of 11 cases among admitted patients at the pediatric hospitals in Dakar, Senegal and to lastly measure the performance of RDT and microscopy in malaria diagnosis using PCR as gold standard.

2. MATERIALS AND METHODS

2.1 Study Design and Patient's Recruitment

A bi-centric, observational, prospective and descriptive study was carried out from June 2018 to January 2019 (8 months) in pediatric patients attending two university hospitals in Dakar, Senegal: Aristide Le Dantec university hospital

and Albert Royer university hospital. Aristide Le Dantec university hospital is a tertiary hospital as well as Albert Royer university hospital with respectively a capacity of 57 beds and 170 beds.

Pediatric patients who met the following inclusion criteria were enrolled: < 18 years old, malaria infection confirmed by rapid diagnostic test (RDT) or microscopy, ARF defined by anuria or oligo-anuria and decrease in glomerular filtration rate (GFR) calculated by the "Bedside Schwartz" formula (2009) [10]. Patients younger than 18 years old, with history of diarrhea, previous chronic or acute renal failure before being infected by malaria and other causes of renal failure were not included in the study.

2.2 Diagnosis of Malaria and Acute Renal Failure

Malaria diagnosis was performed using rapid malaria antigen test (SD- Bioline Malaria Ag Pf) and confirmed by microscopic examination of the parasite by Giemsa-stained peripheral blood with thick and thin blood smears made in the same slide. The patients were followed-up and monitored with measurements of serum creatinine and uremia. Information regarding blood pressure, body weight, antimalarial treatment and other drugs administered were also collected as well as sociodemographic data and anamnesis of medical history, surgical history and phytotherapy. ARF diagnosis was confirmed by the acute decrease (less than 3 months) of GFR according to age of the child.

2.3 PCR for Diagnostic Confirmation and Species Typing

For PCR essay, parasites deoxyribonucleic acid (DNA) was extracted using the QIAamp blood kit (QIAGEN™) according to the manufacturer's instructions, from the collected venous blood in EDTA tub at the admission. For malaria parasites species typing, nested PCR was carried out as previously described [11]. Briefly, the first amplification targeted the *Plasmodium* genus using the primer pair rPLU5 and rPLU6 while the second reaction was performed for the specific detection of the different *Plasmodium* species using a set of two primer pairs (Table 1).

For revelation, PCR products was subjected to gel electrophoresis on a 2% agarose gel, stained with ethidium bromide and visualized under UV light (Supplementary materials).

2.4 Statistical Analysis

Data were collected with the MS Excel 2016 and transferred in Epi-info 7 for analysis. The following formulas have made it possible to calculate the diagnostic parameters (sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV):

- Sensitivity = TP/(TP + FN);
- Spécificité = TN/(TN + FP);
- VPP = TP/(TP+FP);
- VPN = TN/(FN+TN) with TP = true positive, FN = false negative, TN = true negative, FP = false positive and TN = true negative.

3. RESULTS

During the study period, 4,474 children were hospitalized. Among them 130 were infected by malaria parasites

Table 1. Primer pairs for identification of *Plasmodium* species

Primer pairs	Sequences (5' ➔ 3')	Target
	First amplification	
rPLU5	5' -CCT GTT GTT GCC TTA AAC TTC-3'	*Plasmodium* genus
rPLU6	5' -TTA AAA TTG TTG CAG TTA AAACG-3'	
	Second amplification	
rFAL1	5' -TTA AAC TGG TTT GGG AAA ACC AAATAT ATT-3'	*Plasmodium falciparum*
rFAL2	5' -ACA CAA TGAACT CAA TCA TGA CTA CCC GTC-3'	
rVIV1	5' -CGCTTCTAGCTTAATCCACATAACTGATAC-3'	*Plasmodium vivax*
rVIV2	5' -AAG GAA AGA AAG TCC TTA-3'	
rMAL1	5'-ATA ACA TAG TTG TAC GTT AAG AAT AAC CGC-3'	*Plasmodium malariae*
rMAL2	5'-AAA ATT CCC ATG CAT AAA AAA TTA TAC AAA-3'	
rOVA1	5'- GGA AAA GGA CAC ATT AAT TGT ATC CTA GTG-3'	*Plasmodium ovale*
rOVA2	5'-ATC TCT TTT GCT ATT TTT TAG TAT TGG AGA-3'	

(RDT and/or microscopy positive) out of which 11 presented ARF corresponding to 8.5% of ARF related to malaria incidence. Affected children were aged between 2 and 16 years with a mean age of 11 years and a sex ratio of 0.57. Sociodemographic and biological characteristics of these children during their admissions are shown in Table 2.

For malaria diagnosis, RDTs were positive for all patients while microscopy only revealed 6 cases (54.5%) as well as PCR. However, microscopy and PCR presented two discrepancies (Case NK1 and case NK9). Considering PCR as the gold standard tool, RDT showed a relative high sensitivity (100%) and zero specificity with a positive predictive value (PPV) of 54.6% while microscopy respectively showed a sensitivity and a specificity of 66.7 and 60% (Table 3).

4. DISCUSSION

Because the incidence of ARF related to malaria has increased in LMIC notably in Africa [9] and this incidence is unknown or is underestimated in children in Senegal, this present study aimed to determine the incidence of ARF related to malaria in a series of eleven cases among admitted patients in pediatric hospitals from Dakar, Senegal.

Our results showed an incidence of ARF related to malaria at 8.5%. In different populations, malaria contributes 2-39% to the overall hospital admissions for ARF [12]. A previous study in the same study sites found a higher prevalence of 41.8% in a period covering four years between 2011 and 2014 [13]. Elsewhere in sub-Saharan countries, higher prevalence of 21.73% and 23.6% were found by studies carried out in Lomé, Togo and in Kinshasa, democratic republic of Congo, respectively [8,14] while lower prevalence of 0.7% was revealed by a study conducted in Libreville, Gabon between January, 1 2016 and September, 30 2017 [6]. Mishra and Das [12] explained the wide variation by its dependence on age and immunity against malaria. Indeed, the latter is depending on malaria transmission intensity. Thus, ARF related to malaria is considered predominant in older children and adults, particularly in non-immune adults from areas of low intensity of malaria transmission.

Table 2. Sociodemographic and biological characteristics of children suffering from acute renal failure related to malaria (n = 11)

Parameters		NK1	NK2	NK3	NK4	NK5	NK6	NK7	NK8	NK9	NK10	NK11
Sociodemographic	Sex/Age (years)	F/11	F/7	M/7	M/10	F/15	F/16	F/13	M/14	F/13	F/12	M/2
Hematological	Hb (g/dl)	7.3	9.9	7.7	8.7	7.8	3.4	7.7	13.7	3.7	9.1	3.2
	H_T (%)	21.4	29.5	18.6	18.6	24.1	10.1	41	41	24.1	19.8	9.6
	PLT (10^3/ mm^3)	91	50	50	45	560	887	681	560	236	650	10
Renal	Uremia (g/l)	2.53	0.38	2.9	1.5	2.8	0.8	2.9	2.4	3.9	0.31	0.3
	Serum creatinine (mg/l)	88	8	170.9	25.3	183.1	28.8	170.9	90	286.1	6.7	4.1
	GFR (ml/mi 1.73m^2)	7.04	67.1	3.7	21.2	3.8	24	3.2	7.2	2.4	82.8	62.5
Serum electrolytes	Natremia (mEq/L)	124	126	136	123	126	134	136	129	3.9	136	UA
	Kaliemia (mEq/L)	4.5	3.7	3.8	3.4	5.2	3.4	3.9	3.9	5.1	3.8	UA
Parasitological	RDT	+	+	+	+	+	+	+	+	+	+	+
	Microscopy	_	+	+	+	_	_	+	+	_	_	+
	PCR	*Pf*	*Pf*	_	*Pf*	_	_	_	*Pf*	*Pf*	_	*Pf*

F: female; M: male; Hb: Haemoglobin; H_T: Haematocrit; PLT: Platelet; GFR: Glomerular filtration rate; RDT: Rapid diagnostic test; PCR: Polymerase chain reaction; Pf: Plasmodium falciparum; NK: Identification code; UA: unavailable; +: Positive; -: Negative

Regarding age, our findings confirm this predominance of ARF related to malaria in older children showing occurrence predominantly in children between the ages of 10 and 16 years. Only one patient (case NK11) was aged under five years. This is in phage with previous studies notably in Senegal [13] and in Gabon [6].

Using PCR as the gold standard for malaria diagnosis confirmation, RDT showed a relative high sensitivity (100%). However, RDT specificity was nil. This again raises the false positive issues with RDTs as discussed above [3]. The persistence of the HRP2 antigen sometimes until two weeks after treatment may explained these false positives results with RDTs [2]. On the other hand, microscopy showed a sensitivity and a specificity of 66.7 and 60%, respectively. These performances of microscopy are relatively low compared to previously found result which revealed a sensitivity of 93.2% and a specificity of 100%. At least two reasons could explain this weak performance of microscopy: The very low number of tests realized and also the quality of microscopists. Indeed, in the study by Diallo et al. [2] microscopists were WHO-certified level 1 microscopists in the laboratory while these latter were not available on staff at all times notably during on-call period. In addition, several cases of this present study were referred from peripheral health facilities where microscopists are lack of trained.

Only one species, *P. falciparum* was identified in all patients, confirmed by PCR. Yet, renal complications associated with malaria are known from *P. malariae* [5]. This is the case of quartane nephritis which corresponds to a severe glomerular involvement after several years of chronic infection with *P. malariae*. Moreover, a case of acute kidney injury associated with *P. malariae* infection was reported previously by the authors of this present study [15]. However, in Senegal, the distribution of these two plasmodial species, 99% and 1% respectively for *P. falciparum* and *P. malariae* [16] could justify this exclusive presence of *P. falciparum*. In addition, the severity of malaria is generally related to the number of parasitized red blood cells [17]. Therefore, it seems normal that *P. falciparum*, the species presenting the highest parasitaemia is the most found in severe forms of malaria such as renal failure.

Organic renal failure, related to acute tubular necrosis results from obstruction of endothelial cells (intercellular adhesion molecule 1, CD36, thrombospondin), the expression of which is enhanced by the production of cytokines, a consequence of monocytic activation. This

Table 3. Performance characteristics of microscopy and RDT compared to PCR as gold standard

		PCR	
	Positive	**Negative**	**Total**
RDT			
Positive	6	5	11
Negative	0	0	0
Total	6	5	11
Sensitivity (%)	100		
Specificity (%)	0		
PPV (%)	54.5		
NPV (%)	NA		
		PCR	
	Positive	**Negative**	**Total**
Microscopy			
Positive	4	2	6
Negative	2	3	5
Total	6	5	11
Sensitivity (%)	66.7		
specificity (%)	60		
PPV (%)	66.7		
NPV (%)	60		

PCR: Polymerase chain reaction; RDT: Rapid diagnostic test; PPV: Positive predictive value; NPV: Negative predictive value; NA: Not applicable

phenomenon of cytoadherence would only be observed in the cases of infection with *P. falciparum* species [18].

5. CONCLUSION

This study showed the relatedness between ARF and *P. falciparum* malaria. Even though microscopy remains the gold standard for the diagnosis of malaria but microscopists must be regularly trained. In addition, RDT should always be confirmed by microscopy and preferably by the polymerase chain reaction.

CONSENT

The patients were invited and freely consented to participate in the study via their guardians.

ETHICAL APPROVAL

This study was conducted in accordance with the Declaration of Helsinki. To respect the confidentiality, an identification code was assigned to each patient (NK + number). This study was a hospital-based research conducted in routine conditions.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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