

Ionic Disorders in Malaria and Dengue Co-Infection

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Abstract

Introduction: The aim of this study was to investigate ionic disorders in malaria and dengue co-infection at Ouagadougou, Burkina Faso.

Material and methods: This is a descriptive cross-sectional study with retrospective data collection, carried out in the laboratory of the Pediatric University Hospital Charles de Gaulle in Ouagadougou, Burkina Faso, from January 1st, 2017 to December 31st, 2019. The study was on patients who performed a thick blood drop/smear, dengue serology and blood ionogram.

Results: On 1405 cases included in the study, 102 patients (7.26%) were confirmed of malaria. Dengue serology was positive in 235 patients (16.72%). The frequency of co-infection was 1.14% (n=16). The mean age of the patients was 9.93 years and the age group of 0 to 15 years represented 78.93% of the cases. There was a male predominance with a sex ratio (M/F) of 2.58. Hyponatremia (40%), hypocalcemia (40%), hypokalemia (30%) and hypophosphatemia (30%) were the main blood ionogram disturbances in malaria and dengue co-infection. The statistically significant disturbances in case of malaria and dengue co-infection were the absence of hypobicarbonatemia (p=0.036).

Conclusion: Malaria and dengue are responsible for significant morbidity and mortality in Burkina Faso. Although co-infection was rare in the study (1.14%), it was associated with several blood ionogram disturbances. Evaluation and consideration of these disturbances during treatment would contribute to a better care of patients.

Keywords: pediatric university hospital, co-infection, dengue, blood ionogram, malaria

1. Introduction

Malaria and dengue are vector-borne diseases, which are public health problems worldwide and particularly in Burkina Faso. According to the World Health Organization (WHO), malaria was responsible for 228 million cases in 2018 with 405 000 deaths, mostly among children under five years old (World Health Organization [WHO], 2019). Similarly, more than 390 million dengue virus infections occur worldwide each year, with 5.2 million cases reported to WHO in 2019 (WHO, 2021). Both diseases are found in common geographical areas, especially in the tropics and subtropics, and cases of co-infection are increasingly reported (Epelboin et al., 2012; Faruque et al., 2012; Mohapatra et al., 2012; Baba et al., 2013; Mendonça et al., 2015). In Burkina Faso, a survey on 264 children revealed 18 positive cases of dengue, including 10 cases associated with malaria (Ministry of Health, 2014). In 2017, out of 51 cases of dengue observed in the infectious disease department of the University Hospital Yalgado Ouédraogo at Ouagadougou, a co-infection with malaria was observed in 7 patients (Savadogo et al., 2017). These diseases are related to high morbidity, and in endemic areas, complications are responsible for a high number of deaths. The main complications arise from changes in certain haematological and biochemical characteristics, which can aggravate the clinical picture, but also from the immune response against the parasitized red blood cells or against the dengue virus. Thus, some biological complications may be

life-threatening, such as severe thrombocytopenia, severe hepatitis, renal failure and potentially serious ionic disorders. These complications must be detected in the laboratory and treated appropriately to ensure patient survival.

In Burkina-Faso, few studies focused on the biological complications of malaria and dengue co-infection, particularly hydro-electrolytic disorders, making this study necessary. Thus, we studied the disturbances of blood ionogram in malaria and dengue co-infection at the pediatric university hospital Charles de Gaulle in order to allow a better care of the patients.

2. Material and Methods

The study was conducted in the medical analysis laboratory of the University Hospital Charles de Gaulle at Ouagadougou, Burkina Faso. It was a descriptive cross-sectional study, with retrospective data collection on a period of three (03) years, from January 1st, 2017 to December 31st, 2019. The population studied consisted of all patients (all ages) who had a thick blood drop/screen, dengue serology and biochemical examinations including blood ionogram. Sampling was systematic and exhaustive during the study.

The thick blood drop and the blood smear were performed on a slide from a capillary blood sample, stained with Giemsa and May-Grünwald Giemsa respectively. The thick drop was used to make a positive diagnosis of malaria; the blood smear was used to diagnose the species and to evaluate the parasite density. Dengue serology and biochemical assays were performed on venous blood samples collected in dry tubes, centrifuged at 3500 rpm for 5 minutes with serum collection. The SD Bioline Dengue Duo kit (Standard Diagnostics) was used for the diagnosis of dengue and was considered as a probable case of dengue, any patient with a positive serology for NS1 antigen and/or immunoglobulin M. Blood ionogram parameters were represented by the serum determination of sodium, potassium, chlorine, calcium, magnesium, phosphate and proteins, using the Indiko Plus automaton (Thermo Fisher Scientific). The values obtained were interpreted according to the patient's age.

Data collected on a questionnaire were entered from Microsoft Office Excel 2013 software and analyzed with Epi-Info™ 7 software in its version 7.2.0. Univariate and bivariate regression analyses were performed to establish a statistical relationship between the variables. For univariate analysis, Chi-2 or Fischer tests were used and for bivariate analysis, measures of association such as Odds Ratio and p-value were performed. The significance level was $p < 0.05$. Before the beginning of the study, a request for authorization to collect data was obtained from the management of the Pediatric University Hospital Charles de Gaulle. Data confidentiality was maintained throughout the study.

3. Results

A total of 1405 subjects were included in the study.

3.1 Socio-Demographic Characteristics

The mean age of the patients of the study was 9.93 ± 10.26 years with extremes from 1 day to 80 years. The age range of 0 to 15 years was the majority with 1109 patients, representing a frequency of 78.93%. Male sex was the most represented with a sex ratio of 1.15. The sociodemographic characteristics are presented in Table 1.

Table 1. Distribution of patients according to socio-demographic characteristics

Characteristic		Number	Percentage (%)
Age (years)	≤ 15	1109	78.93
] 15-30]	138	9.82
] 30-45]	121	8.61
	> 45	37	2.63
Gender	Male	752	53.52
	Female	653	46.48

3.2 Prevalence of Malaria, Dengue and Co-infection

Thick blood tests were positive in 102 patients, i.e. a prevalence of malaria of 7.26%. The mean parasite density was 30163.93 ± 67741.85 trophozoites/ μL , ranging from 110 to 520 909 trophozoites/ μL . Dengue serology was positive in 235 patients (16.72%). Out of the 1405 patients, the frequency of malaria-dengue co-infection was 1.14% with $n=16$ (Figure 1).

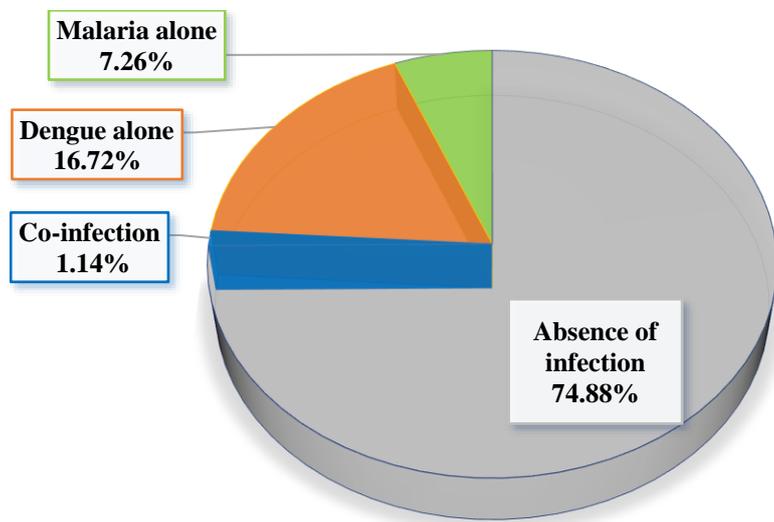


Figure 1. Frequency of malaria, dengue and co-infection

3.3 Blood Ionogram Results

3.3.1 Mean Values of Blood Ionogram Parameters

Table 2 presents the mean values obtained after the determination of the different parameters of the blood ionogram, according to the cases of co-infection, dengue or malaria.

Table 2. Mean values of blood ionogram parameters

Parameters	Co-infection	Dengue	Malaria
Natremia (mmol/L)	135.44 ± 08.09	134.71 ± 05.57	134.94 ± 05.90
Kalemia (mmol/L)	3.65 ± 0.44	4.35 ± 0.80	4.30 ± 0.66
Calcemia (mmol/L)	2.26 ± 0.29	2.35 ± 0.35	2.33 ± 0.48
Chloremia (mmol/L)	104.02 ± 04.71	99.87 ± 11.74	104.61 ± 4.54
Phosphatemia (mmol/L)	1.22 ± 0.41	1.55 ± 0.46	1.32 ± 0.73
Magnesiumemia (mmol/L)	0.80 ± 0.40	0.76 ± 0.31	0.71 ± 0.24
Bicarbonate (mmol/L)	23.89 ± 3.48	21.74 ± 4.21	19.69 ± 4.26
Protidemia (g/L)	72.64 ± 11.65	72.21 ± 11.58	66.4 ± 11.75

3.3.2 Frequency of disturbances

The frequencies of blood ionogram disturbances are presented in Figure 2. In case of malaria-dengue co-infection, the main disturbances were hyponatremia (40%), hypokalemia (30%), hypocalcemia (40%) and hypophosphatemia (30%).

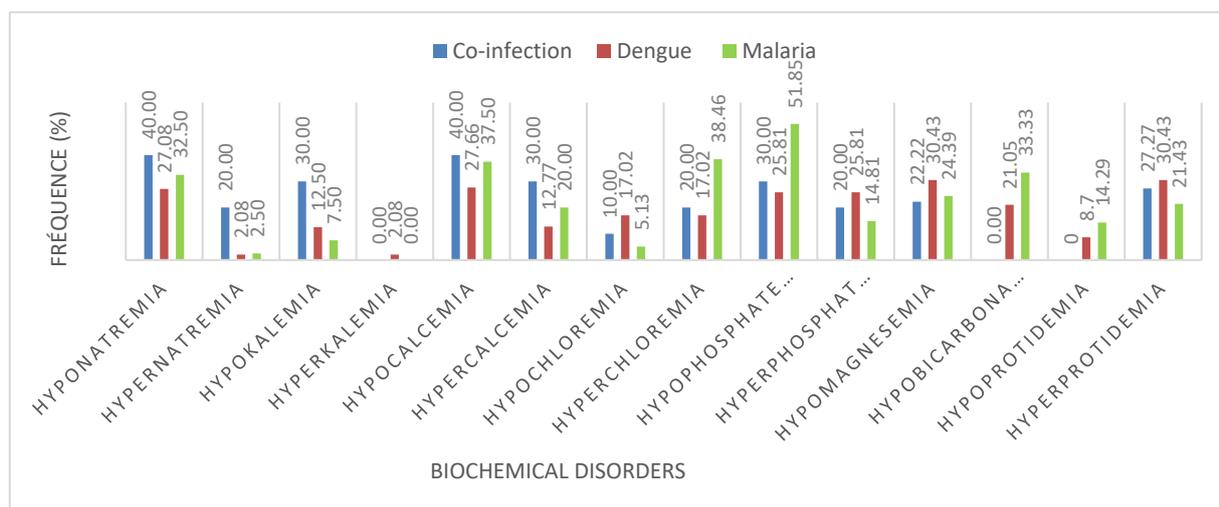


Figure 2. Frequency of blood ionogram disturbances

3.3.3 Univariate Analysis

In univariate analyses, the absence of hypobicarbonatemia ($p=0.036$) was significantly associated with malaria-dengue co-infection.

No abnormality was associated with the presence of dengue alone. Hypobicarbonatemia ($p=0.048$), hyperchloremia ($p=0.013$) and hypophosphatemia ($p=0.043$) were present in malaria infection alone (Table 3).

Table 3. Univariate analysis of blood ionogram disturbances between co-infection, dengue and malaria

Disturbances	Co-infection	Dengue	Malaria
Hypobicarbonatemia	0.036	0.280	0.048
Hyponatremia	0.250	0.230	0.370
Hyperchloremia	0.350	0.060	0.013
Hypercalcemia	0.150	0.290	0.590
Hypomagnesemia	0.770	0.500	0.650
Hypophosphatemia	0.330	0.130	0.043
Hypokalemia	0.440	0.450	0.340
Hyperprotidemia	0.450	0.490	0.360

3.3.4 Bivariate Analysis

Among biological disturbances, hypophosphatemia was less frequent in the co-infection group than in the malaria-only group (OR= 0.24; CI95%: 0.06-0.99; p -value = 0.044). On the contrary, hypophosphatemia was more common in the co-infection group than in the dengue-only group (OR = 7.04; CI95%: 1.52-32.63; p -value = 0.009).

4. Discussion

The aim of the present study was to investigate blood ionogram disturbances in malaria and dengue co-infection at the Pediatric University Hospital Charles de Gaulle. Despite the retrospective nature of the study with the fact that some clinical records were not complete, 1405 patients were included.

4.1 Prevalence of Malaria And Dengue Co-Infection

The prevalence of the co-infection in this study was 1.14% (Figure 1), thus relatively low. In a study at Thaïlande, on 194 dengue patients, no association with malaria has been found (Singhsilarak et al., 2006). Even if the phenomenon of co-infection seems to be rare in terms of frequency (Abdul-Ghani et al., 2021), it is often described in the literature. Thus, Im et al. identified in their study 39 cases of co-infection in 2762 patients, i.e. a frequency of 1.4%; thus similar to our results (Im et al., 2020). The low frequency (1.14%) could be explained by the fact that the study was limited to results recorded only in the laboratory. It could also be due to low recording of the results of thick blood drop in the registers of

the parasitology department, but this remains to be confirmed with further studies. In addition, the study period did not coincide with dengue outbreak as the one which occurred in the city of Ouagadougou in October 2016; this epidemic being considered as the biggest of its history (Im et al., 2020; Lim et al., 2021). On the other hand, Mohapatra et al. reported a higher frequency of 7.4% in 2012 in India (Mohapatra et al., 2012). In Burkina Faso, few data are available on malaria and dengue co-infection (Ministry of Health, 2014; Savadogo et al., 2017; Im et al., 2020), except for some doctoral theses which found co-infection frequencies of 20.4% in 2017 (Ly, 2017) and 55.24% in 2020 (Kane, 2020). The high prevalence of these studies may be explained by the methodology used, which included patients with only Ig G positivity in dengue cases. However, the presence of Ig G is most often a sign of old dengue and only titration could distinguish it from secondary dengue. All cases of positive Ig G alone were excluded from this present study, as titration was not available.

4.2 Ionic Disorders

Many studies focused on the biological aspects of malaria and dengue co-infection (Epelboin et al., 2012; Mohapatra et al., 2012; S. Ahmad et al., 2016; Shah & Mehta, 2017; Kotepui & Kotepui, 2019; A. Ahmad et al., 2019; Kotepui et al., 2020; Galani et al., 2021), but very few noted ionic disturbances. The present study highlighted numerous blood ionogram disturbances during the concomitant presence of malaria with dengue (Figure 2). However, the lack of evidence in the literature on the hydroelectrolytic disorders encountered during coinfection considerably limits discussion.

Hyponatremia was found in 40% of co-infected patients, in 27.08% of dengue cases alone and 32.5% of malaria cases. Regarding the results of dengue, Vachvanichsanong and McNeil found 46.7% of hyponatremia (Vachvanichsanong & McNeil, 2015). Epelboin noted that 7.1% of patients co-infected with dengue and malaria had hyponatremia (Epelboin et al., 2012). In the literature, hyponatremia is the most common biochemical disturbance in dengue or malaria (Karnad et al., 2018; Rehman et al., 2020; Ng & Cheong, 2021); but insufficiently documented in co-infection. However, on the one hand, this may be explained by an excess of water due to an increase in metabolism, an inappropriate transient secretion of antidiuretic hormone leading to an increased tubular reabsorption, an influx of sodium into the cells due to a dysfunction of the sodium-potassium pump, or a combination of these factors; and on the other hand by digestive losses of sodium (diarrhea, vomiting). Indeed, Kane noted 38% of patients presenting digestive signs as vomiting and diarrhea, responsible for extracellular dehydration leading to a significant hyponatremia (Kane, 2020).

Hypokalemia was present in 30% of patients with co-infection (Figure 2). It could be attributed to activation of the renin-angiotensin-aldosterone system resulting in loss of potassium in the urine. In contrast, hyperkalemia was absent in co-infection but only found in one patient (2.08%) infected with dengue alone. These results are similar to those of Epelboin who recorded 1.5% in his study (Epelboin et al., 2012). Vachvanichsanong and McNeil reported an hyperkalemia of 5.95% (Vachvanichsanong & McNeil, 2015). This hyperkalemia could be explained on the one hand by the presence of metabolic acidosis and on the other hand by the altered renal function of some patients.

Hypocalcemia was present in 40% of patients with co-infection, 27.66% and 37.50% in isolated dengue and isolated malaria respectively (Figure 2). Hypocalcemia, although insufficiently reported in co-infection, is particularly well documented in dengue (Bunnag & Kalayanarooj, 2011; Kapoor & Singh, 2012; Constantine et al., 2014) and malaria (Ayoola et al., 2005; Aijazi et al., 2020). Hypocalcemia is observed in severe dengue and is thought to be associated with increased mortality. Hypercalcemia was found in 30% of co-infected patients, compared to 37.50% for malaria mono-infection and 27.66% for isolated dengue. Hypercalcemia could be explained by an excess of intravenous calcium intake or by the altered renal function of some of the patients. Calcium remains an important parameter to avoid cardiac complications.

Hyperchloremia was observed in 38.46% of malaria cases, 17.02% for dengue and 20% in case of co-infection (Figure 2). The results are similar to those of Syed et al. who demonstrated that serum chloride levels in dengue patients significantly increase (Syed et al., 2014). This observed hyperchloremia could be due to the extracellular dehydration of the patients due to vomiting, but also to the decrease of bicarbonates.

We reported hypophosphatemia in 30%, 25.81% and 51.85% of patients respectively with co-infection, dengue and malaria. Likewise, hypomagnesemia was found in 22.22% of co-infected patients, 24.39% with malaria and 30.43% of those suffering from dengue. Hypophosphatemia and hypomagnesemia could be explained by the presence of hypercalcemia and the renal dysfunction of some of our patients.

No cases of decreased bicarbonate ions or hypoprotidemia were noted during the study. However, 27.27% of cases of hyperprotidemia were present in case of co-infection, versus 21.43% for malaria and 30.43% for dengue. It could be explained by the presence of hemoconcentration due to digestive losses (vomiting, diarrhea).

5. Conclusion

Malaria and dengue are the two major stars of tropical infectious diseases and are endemic in Burkina Faso. Both diseases

can be diagnosed in the same patient and the present study found a co-infection frequency of 1.14%. It was found that the ionogram disturbances were dominated by hyponatremia, hypocalcemia, hypokalemia and hypophosphatemia. It seems appropriate that further studies be carried out to assess the correlation of these ionic disorders with the evolution of patients with malaria-dengue co-infection.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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