Importance of clinical and laboratory profiles for the differential diagnosis of malaria and acute viral hepatitis

Cacyane Naiff do Amaral,1 Yael Duarte de Albuquerque,2 Ana Yecê das Neves Pinto,3 José Maria de Souza4

Abstract

Objective: To establish clinical and diagnostic findings of malaria and acute viral hepatitis in children, stressing similarities and differences, so as to enhance the sensitivity of early malaria diagnosis in childhood.

Methods: Two groups were studied, each including 30 children between 2 and 10 years of age. The patients presented either primary malaria infection or acute viral hepatitis, confirmed by thick blood film and tests for markers of viral hepatitis A and B. The patients were submitted to the following evaluations: erythrocyte, leucocyte and platelet counts, hemoglobin and hematocrit dosage, hepatic enzymes, urea, creatinine and bilirubin dosage. Clinical and laboratory findings were described for both groups and compared. Individuals with alterations on the physical exam in both groups were compared using Fisher’s exact test.

Results: Baseline clinical findings were the same in all patients: fever, headache, digestive problems and dark urine. One half of malaria patients did not present the classical malaria signs, but all of them presented fever, differently from patients with hepatitis. In malaria patients, anemia and thrombocytopenia were significantly more frequent than in hepatitis patients. A remarkable increase of bilirubin and hepatic enzyme levels was found in hepatitis patients.

Conclusions: A detailed physical examination and a thorough evaluation of non-specific laboratory tests are sufficient to allow the presumptive diagnosis of both malaria and viral hepatitis, and to reinforce the early diagnosis and treatment of malaria.

Introduction

The elevated incidence of malaria in the Amazon region makes this diagnosis an obligatory clinical suspicion for all health professionals in any febrile case coming from the region. In contrast, the eradication campaigns developed up to 1992 by the now defunct Superintendancy of Public Health Campaigns (SUCAM - Superintendência de Campanhas de Saúde Pública) encouraged a policy of “monopoly on malaria activities” on the part of the technical management of the eradication programs, promoting total ignorance of the innumerable details relating to malaria in the Amazon region on the part of the majority of health professionals active in the area today.

It respect of clinical factors, for example, it is known that the clinical manifestations of malaria are easily confused with other diseases, when jaundice appears, it is more common that diagnosis is confused with hepatitis, leptospirosis and yellow fever.1-4

A study performed by Almeida Netto et al. involving 102 severe malaria sufferers due to Plasmodium falciparum, found that 40% of the patients were misdiagnosed with a lethality of 40%. Of the incorrect diagnoses, hepatitis was the most common, in 30% of cases.3

The study cited is just one more, of many, which prove the diagnostic confusion existing between hepatitis and malaria, leading to frequent diagnostic equivocation in malaria cases which are erroneously treated as hepatitis.5

Clinical experience proves that children are the population band that most often suffers from the consequences of the diagnostic confusion between malaria and acute viral hepatitis, since within this age group in particular the disease often does not manifest the classical trio of symptoms of fever, headaches and shivering.6,7

The authors evaluated the clinical and laboratory profile of malaria and acute viral hepatitis in two groups of children, concomitantly, highlighting the similarities and differences between them in the hope of thus reiterating their clinical and laboratory presentations and minimize the frequently occurring confusion between them.

Methods

Sixty patients of both sexes were analyzed in a prospective manner drawn from those who spontaneously sought care within the municipality of Belém at the Malaria Trials Program (Programa de Ensaios em Malária - PEM) or the Hepatopathy Unit at the Instituto Evandro Chagas (IEC) and who met the following criteria for inclusion: 1) Primary infection - malarial or acute viral hepatitis, confirmed by specific laboratory tests performed on the first day of clinical care; 2) Age group between two and ten years of age, 3) Consent form signed by parent or guardian permitting participation.

The children were split into two groups, 30 (thirty) patients were carrying malaria and 30 (thirty) acute viral hepatitis. All were cared for at the PEM/IEC and their clinical and laboratory evaluation took the following form:

Clinical assessment: performed on the first day of care (D0 - day zero), including anamnesis - in which was investigated, in addition to other details, the day on which symptoms began (OD - onset day) -; investigation of epidemiological data; general and specific physical examinations and completion of the appropriate form.

Laboratory assessment: specific diagnosis was confirmed in malaria cases by plasmodium thick blood film assay stained by the Walker method and in hepatitis cases, by tests for viral hepatitis markers A, B and C (HBs Ag, Anti-HBs, total Anti-HBc, Anti-HBc IgM, Anti-HAV IgM and Anti-HCV) by the ELISA method. Each group of patients was submitted for both the plasmodium assay and the viral markers for hepatitis diagnosis. Non-specific examinations were: hemagram, platelets count, urea, creatinine, aminotransferases (alaninaminotransferase - ALT and arginine aspartataminotransferase - AST), total bilirubin and fractions, alkaline phosphatase (AP) and gamma-glutamilitransferase (GGT).

Definitions: Mild fever: axilliary temperature of 37.5 to 38° C; moderate fever: axilliary temperature of 38.5 to 39° C; high fever: axilliary temperature above 39° C; anemia - in children less than 6 years old, hemoglobin levels below 11.0 g/dl, in children between 6 and 10 years old, hemoglobin levels lower than 12.0 g/dl (female sex) and lower than 13.0 g/dl (male sex); thrombocytopenia: platelet count lower than 180,000, lymphopenia: lymphocyte count (total) lower than 1,000/mm³.

Clinical and laboratory data was processed on a dedicated database with the help of Epi Info version 6.03. The proportion of the children presenting with manifestations common to both pathologies were statistically compared using Fisher’s exact test.

The Ethics Committee at the Instituto Evandro Chagas approved this study.

Results

Fifteen (50%) of the malaria patients referred to the classical trio (fever, headaches and shivering) as the first symptoms of the pathology. Of these, 11 remained in this state for an average of 6.2 days. In these cases the fever (isolated or associated with the other symptoms) occurred in 100% of the patients and manifested with elevated intensity in 24 children (80%) and in the remainder (20%) presented as mild or moderate.

Among the acute hepatitis cases, 22 children (73.3%) presented fever at the onset of the disease and of these just six (20%) still had fever when the disease had run its course (7.3 days on average). Four patients (13.3%) presented high fever accompanied by headaches; three patients (43.3%)
presented moderate fever; five (16.6%) referred to mild fever and eight (26.6%) did not present fever.

It was observed that, among the malaria patients, gastrointestinal manifestations such as epigastric pain (63.3%), nausea (56.6%) and vomiting (53.3%), while common, presented with mild or moderate intensity, not lasting for more than five days nor causing dehydration or making feeding impossible. Similar findings occurred with the hepatitis patients (epigastralgia - 73.3%, nausea - 83.3%, vomiting - 76.6%).

The principal alterations revealed by physical examination for the two groups are laid out in Table 1. Comparing the two groups it was observed that the malaria sufferers presented greater occurrence of pallid conjunctiva, cutaneous pallor and splenomegaly in relation to the hepatitis patients. The occurrence of sclerotic jaundice was more in evidence among the hepatitis patients.

Table 2 shows the frequency of anemia and thrombocytopenia for the two groups. These two basic findings were significantly more frequent among the malaria patients. The main alterations (elevated levels) found upon biochemical examination can be found in Table 3. The hepatitis suffersers presented elevated levels of AST, ALT, total bilirubin (primarily the direct fraction), alkaline phosphatase and GGT at proportions of above 70% occurrence. Urea and creatinine assay results were normal for both groups. Table 4 shows total bilirubin levels and fractions in patients with malaria and hepatitis. The sample studied revealed malaria sufferers with no significant bilirubin alterations and hepatitis patients with hyperbilirubinemia at the cost of the direct fraction.

The malaria patients’ diagnoses were confirmed over a timescale which varied from 2 to 60 days, with an average of 13.2 days. Seven malaria patients (23.3%) had received previous medical attention, including between one and five consultations, at which they received medication for their symptoms. They had sought attention for a plasmodium assay on their own initiative without having received medical direction to do so.

Three of the malaria patients had undergone at least one thick blood film plasmodium assay with negative results, without previous antibiotic therapy.

One of the malaria sufferers who had been ill for just two days, was diagnosed with malaria by P. vivax and was in a generally satisfactory condition, receiving specific medication. On the second day of treatment the patient’s status worsened, loss of consciousness attainment malaria coma, and in a thick blood film examination, erythrocyte forms of P. falciparum (mixed malaria) were detected. The patient required hospitalization and recovered well after specific therapy was instituted for P. falciparum.

---

**Table 1** - Frequency of alterations revealed by physical examination of 60 malaria or acute viral hepatitis patients

<table>
<thead>
<tr>
<th>Physical examination findings</th>
<th>No. of patients with positive findings</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malaria</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Pallid conjunctiva</td>
<td>26 (86.6%)</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Sclerotic jaundice</td>
<td>3 (10%)</td>
<td>18 (60%)</td>
</tr>
<tr>
<td>Cutaneous-mucosa jaundice</td>
<td>0</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Cutaneous pallor</td>
<td>23 (76.6%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>13 (43.3%)</td>
<td>17 (56.6%)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>15 (50%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Fisher’s exact test: p values < 0.05 were considered significant.

**Table 2** - Number of patients with anemia and thrombocytopenia among 60 patients with malaria or acute viral hepatitis

<table>
<thead>
<tr>
<th>Laboratory alterations</th>
<th>No. of patients</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malaria</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Anemia</td>
<td>26 (86.7%)</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>23 (76.7%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Fisher’s exact test: p values < 0.05 were considered significant.

**Discussion**

The children are from the age group which pays the heaviest tribute to malaria. The disease is responsible for between one and two million infant deaths every year. Very often the morbidity and mortality is related to delays in establishing the correct diagnosis as a result of a clinical status which is not always characteristic.
In schoolchildren and adolescents, symptoms are similar to those observed in adults, while, in pre-school children and infants, the clinical expression of the disease is often uncharacteristic, and the trio of fever, shivering and headaches may not be present. Ventura et al. (1999) evaluated the clinical presentation of malaria in 100 children and adolescents and found that the malaria trio only occurred in 13.6% of cases.7

With malaria carriers, when jaundice and particularly choluria appear, it is very common that diagnosis is confused with other diseases, of which hepatitis stands out.3,6,9 The results presented here confirm the presence of signs and symptoms in common between the two infirmities, however, propaedeutic characteristics, properly investigated, are capable of clearly demonstrating the differences between the two, particularly in relation to fever.

According to Ventura et al., fever appears to be a cardinal element in the diagnosis of malaria, occurring with 88% of their sample.7 The results of the current study coincide with this level of occurrence, with the children who were suffering from malaria evolving with fever, generally of moderate to elevated intensity, constant and daily.

With the hepatitis sufferers, despite fever also being a frequent finding, the intensity was mild to moderate and often continued for just the first two or three days, which is a marked difference when compared with malaria in which the patient remains febrile while evolving.4

The digestive symptoms which were encountered in a highly variable manner had no importance in terms of the comparison of samples. In particular, when malaria sufferers were observed to have digestive symptoms associated with choluria, there was often an erroneous suspicion of hepatitis during the diagnostic workup.

The findings from the physical examination of those suffering from malaria were characterized by pallid conjunctival mucosa, cutaneous pallor, hepatomegaly and splenomegaly. In hepatitis cases, cutaneous-mucosa jaundice and hepatomegaly were common.

The results of the evaluation of blood test values were highly divergent, with intense anemia and thrombocytopenia evident among the children suffering from malaria, which

### Table 3 - Number of patients with malaria and acute viral hepatitis that presented elevated levels of aminotransferases, total bilirubin, alkaline phosphatase and gamma-glutamyltransferase

<table>
<thead>
<tr>
<th></th>
<th>AST (U/L)*</th>
<th>ALT (U/L)†</th>
<th>Total bilirubin (mg/ml)</th>
<th>Alkaline phosphatase (U/L)</th>
<th>GGT (U/L) ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>1 (3.3%)</td>
<td>3 (10%)</td>
<td>6 (20%)</td>
<td>5 (16.6%)</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>28 (93.3%)</td>
<td>29 (96.6%)</td>
<td>21 (70%)</td>
<td>28 (93.3%)</td>
<td>28 (93.3%)</td>
</tr>
<tr>
<td>p ¶</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* AST = Arginine aminotransferase (elevated values: > 40 U/l).
† ALT = Alanine aminotransferase (elevated values: > 32 U/l).
‡ GGT = Gamma-glutamyltransferase (elevated values: > 32 U/l).
¶ Fisher’s exact test: p values < 0.05 were considered significant.

### Table 4 - Mean, maximum value and minimum value of total bilirubin and fractions

<table>
<thead>
<tr>
<th>Exams</th>
<th>Mean (mg/ml)</th>
<th>Malaria Maximum value (mg/ml)</th>
<th>Malaria Minimum value (mg/ml)</th>
<th>Hepatitis Maximum value (mg/ml)</th>
<th>Hepatitis Minimum value (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>0.8</td>
<td>1.63</td>
<td>0.47</td>
<td>3.58</td>
<td>12.51</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>0.75</td>
<td>1.3</td>
<td>0.31</td>
<td>1.59</td>
<td>4.87</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>0.14</td>
<td>0.51</td>
<td>0.06</td>
<td>1.94</td>
<td>8.15</td>
</tr>
</tbody>
</table>
coincides with findings reported in literature. Only four of the hepatitis patients presented anemia and none of them evolved with thrombocytopenia.

It is known that with hepatitis urea and creatinine levels often remain normal, however, with malaria sufferers these values can suffer discrete increases at the onset of the disease. In this study there were no urea or creatinine alterations in any of the cases in either of the groups.

With malaria, aminotransferases are generally normal or discretely elevated and very rarely pass 200 U/ml of blood. Among the groups studied, only one child suffering from malaria presented increased AST and three elevated ALT. In contrast, the majority of hepatitis patients had increased aminotransferases.

Bilirubin can be elevated both with hepatitis and malaria. In malaria it is the unconjugated fraction which predominates, due to hemolysis. With hepatitis, the increases occur both in the conjugated and unconjugated fractions, with a predominance of the latter. Correlating clinical and laboratory data which reinforce the most correct diagnostic presumptions, the authors reiterate the sclerotic jaundice findings (denoting significant hyperbilirubinemia) in hepatitis sufferers and their absence in the malaria patients studied.

Alkaline phosphatase and GGT were elevated in a small number of malaria cases and in the majority of the hepatitis patients. The increase in these enzymes is indicative of hepatic cholestasis, and is little altered in cases of viral hepatitis. With malaria, these values are generally normal, however, when there are alterations these are highly discrete, which was corroborated in this study.

The interval of time that passed before establishing a diagnosis of malaria was an average of 13 days, which agrees with findings made by other authors. This fact suggests that there is little familiarity on the part of health professionals with the disease and its clinical characteristics, which makes this situation a cause for concern, since this occurs in an endemic region where a presumptive diagnosis of malaria should be obligatory in all febrile cases, emphasizing any origin from or history of travel to areas of endemic malaria.

Three patients had had previous thick blood film plasmodium assays with negative results. This phenomenon is normally expected to be due to the presence of subpatent parasitemias, a lack of technical ability in reading the slide or previous antibiotic therapy. The importance of insistence on a diagnosis based on clinical status and the origin of the individual, even in the face of previous negative results, must be emphasized.

In the current study, special attention is merited to the case of the child who developed a malaria coma in three days of the disease, and who appeared in a normal state the day before the coma, evolving exceptionally rapidly. Cerebral malaria is one of the most serious forms of the disease and can lead to death in a few hours if treatment is not immediately started.

Previous studies have shown that many malaria patients have their diagnoses delayed as a result of the initial confusion between malaria and hepatitis, especially children.

Clinically, childhood malaria is not as clearly characterized as it is with adults, however, it differs significantly from the clinical and laboratory presentation of acute viral hepatitis. Despite the common, exuberant digestive manifestations associated with choluria in malaria patients, a detailed workup with a definition of the fever, together with non-specific laboratory examination results, interpreted in the correct manner, are enough to differentiate between these two major endemics, and thus establish an early diagnostic suspicion of malaria.

Acknowledgments

For their decisive contributions: Dr. Manoel do Carmo P. Soares, Olglaísio do Socorro C. Souza and Ilton Leandro de Souza of the Hepatopathy Unit at the IEC. To Dr. Manoel Gomes da S. Filho of the Clinical Pathology Unit. Also to Orivaldo de Lima Mota Filho technician at the Fundação Nacional de Saúde/ Instituto Evandro Chagas.

References