Concomitant Infections by Malaria and Arboviruses in the Brazilian Amazon Region[1]

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ABSTRACT: Six cases, in which infections of arboviruses and malaria were observed in the same patient and at the same time, in the Amazon Region of Brazil. The arboviruses isolated are included in family Bunyaviridae, genus *Bunyavirus. Plasmodium. falciparum* (diagnosed by thick and thin smears) was associated with the following arboviruses: Guaroa (California serogroup) 3 times; Tacaiuma (Anopheles A serogroup) twice; Catu (Guama serogroup) once. The latter was also infected by *P. vivax.*

Five patients were male and one female. All were seventeen years old or more. None were born in Pará State, although all were living there. The famale was a domestic helper, while four men were agricultural workers and one was a commercial traveler.

The main clinical history of disease was fever with headache, chills, myalgia and arthralgia. Sometimes we noted abdominal pain, nausea, vomiting and dizziness. Jaundice was recorded in two cases of *P. falciparum* in association with Tacaiuma. The typical periodic fever associated with malaria was not observed. It was continuous. Patients were treated by SUCAM with chloroquine, primaquine, quinine, or other drugs when necessary. Five recovered quickly, but one died.

These cases are important because in Amazonia thousands of people are diagnosed and treated for malaria. About 10% of the strains of *P. falciparum* are considered to be drug resistant. The possibility (probably much underestimated) of concomitant infections with arboviruses may obscure the effectiveness of the treatment, or may lead to an erroneus diagnosis.

It is proposed that the joint infections with malaria and Guaroa or Tacaiuma viruses were due to the fact that in Amazonia, both agents share the same mosquito vectors in forested areas, either *Anopheles nuneztovari* or *A. triannulatus.*

INTRODUCTION

Every year thousands of cases of malaria are diagnosed in Brazil and more than 90% of them, occur in the Amazon Region. At the time of these studies, malaria in Brazil was caused by both *Plasmodium falciparum* and *P. vivax* and the incidence of each parasite was about equal. In the Amazon Basin however, we have a great number of arboviruses capable of causing disease in man. In the forest, *P. falciparum, P. vivax* and some arboviruses have the same potential vectors, mosquitoes of the group *Anopheles (Nyssorhynchus)* mainly *A. (N) triannulatus* and *A. (N.) nuneztovari.* Six cases of fever of unknown origin, were after several examinations diagnosed as malaria, which is the most frequent tropical disease present in the Amazon Region of Brazil. Despite treatment, the symptoms reamined. In these six cases, another agent was found at the same time, and all were arboviruses of the family Bunyaviridae.

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MATERIAL Y METHODS

20 ml blood samples were taken from each patient by venopuncture. Thick and thin smears were made to look for hemoparasites. 0.02 ml of a 1:10 of blood diluted in fresh boratesaline solution of bovine albumin (fraction V) 0.75% and antibiotics, were inoculated intracerebrally (ic) in suckling mice for virus isolation[7]. Serum samples were tested by the Hemagglutination Inhibition test (HI), to detect antibodies to arvobiruses[6]. When indicated, Complement Fixation Test (CF) was also used, mainly to determine the specific serotypes, using the plaque method[2].

All patients with malaria were treated by the Superintendencia de Campanhas de Saúde Pública (SUCAM),

Fig.1 : MAP OF THE AMAZON REGION, SHOWING THE PLACES WHERE CONCOMITANT INFECTIONS OCCURRED.

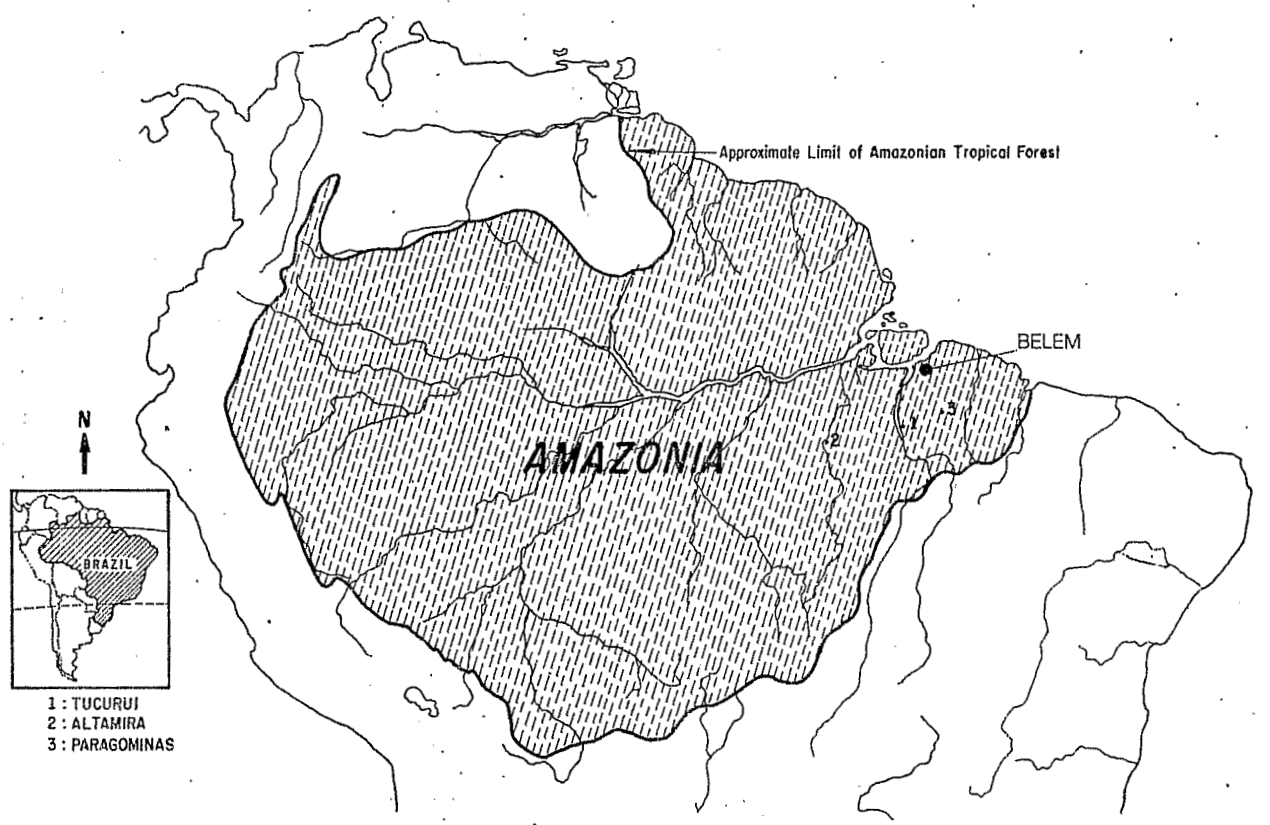

Fig. 1: Map of the Amazon region, showing the places where concomitant infections occurred

Ministry of Health of Brazil, who are responsible for the treatment of malaria in Brazil. The drugs used in the specific treatment were Chloroquine (600 mg 1st day, 450 mg 2nd and 3rd days) and Primaquine (15 mg per day/14 days). If the patient remained positive after treatment for malaria, other schedules were used, as for example an association of either Quinine (1500 mg per day/3-5 days) plus Tetracycline (1000-2000 mg per day/7-10 days) or Sulfaxodine (500 mg per day) plus pyrimethamine (25 mg per day) for 3 days.

Non-specific symptoms were treated with Aspirine (1000-2000 mg daily) or other drugs.

RESULTS

Diagnosis. Guaroa virus (California serogroup) was isolated three times, Tacaiuma virus (Anopheles A serogroup) twice and Catu virus (Guama serogroup) once. All patients had active *P. falciparum* infections and the patient with Catu virus, was also positive for *P. vivax*. Unfortunately, convalescent sera from the patients were not obtained, because these patients lived, either in or, near forested areas which were a long way away from our laboratory in Belém (Figure 1).

TABLE 1
DISTRIBUTION OF 6 CASES OF CONCOMITANT INFECTIONS WITH PARASITES AND ARBOVIRUSES IN AMAZON REGION OF BRAZIL

RECORD	PLACE*	PARASITE	VIRUS	YEAR
H 210353	Paragominas	*P. falciparum*	Guaroa	1971
H 260330	Altamira	*P. falciparum*	Catu	1974
		P. vivax		
H 372559	Altamira	*P. falciparum*	Tacaiuma	1979
H 411166	Altamira	*P. falciparum*	Taciuma	1983
H 428895	Tucurui	*P. falciparum*	Guaroa	1984
H 467925	Tucurui	*P. falciparum*	Guaroa	1987

* All cities are in areas of Para State

Table 1, lists the places from which the patients came, parasites detected and arbovirus diagnosed, as well as the year in which they occurred.

Clinical aspects. Patients were 17 to 37 years old, five were male and one female. The symptoms referred to by

all were fever, chills, headache and myalgia. Other symptoms presented by some were vomiting (5), dizziness (4), arthralgia (3), abdominal pain (2), anorexia (2), jaundice (2), photophobia (2) and lymphadenopathy (1). The two cases of jaundice occurred in patients with *P. falciparum* infections and Tacaiuma. One of them, developed coma, renal and hepatic failures as well as hemolysis (erythrocytes = 1,900,000), anaemia (haemoglobin = 5.0%) and seven days after onset of the disease she died, despite treatment. In the other case, the jaundice decreased and the patient recovered both renal and hepatic functions.

Futhermore, in the other patients, the fever remained until the viral cycle had been completed. On an average, the disease persisted for five days after treatment and, only two patients (both with jaundice) were hospitalized.

DISCUSSION

Concomitance of cases. It is very interesting, that we found two different agents in the same patient at the same time; one being a parasite and the other an arbovirus. Malaria caused by *P. falciparum* was detected six times in association with arboviruses; three times with Guaroa, twice with Tacaiuma and once with Catu. The latter patient was also infected with *P. vivax*.

The concomitance of Tacaiuma and Guaroa must be more frequent than detected. In effect, the potential vector of both are the mosquitoes *A. nuneztovari* and *A. triannulatus*[5]. These arthropods have been found frequently infected with sporozoites of *Plasmodium*, specially *P. vivax* and nowadays are playing an important role in the transmission of malaria in the villages and small towns of northern Brazil[1]. Today *A. nuneztovari* is considered a major vector of malaria in certain areas of the Amazon Region such as Northern Venezuela[3] and Southeast Colombia[4].

The occurrence of Catu and malaria appears to be merely incidental, because this arbovirus has as vectors *Culex* mosquitoes[8] which are not considered to be vectors of malaria.

The small number of mixed cases diagnosed, is possibly because specific diagnosis of arbovirus infections is only made in our laboratory. Once a smear is positive to malaria, nobody normally searches for another pathogen as the causative agent of the disease. It is very dificult to isolate arboviruses, because the blood sample has to be collected, when the viremia is occurring, which means during the first days of disease. Events normally take place in the isolated rural areas of Amazonia and it is difficult to obtain, suitable samples for attempted isolation, because of the necessity of special storage containers to transport the specimens to the laboratory.

Clinical Symptoms. The symptoms presented by the patients with malaria (*P. falciparum*) were the same as had been described. It is intriguing that only the two patients with malaria and Tacaiuma had jaundice. Tacaiuma had been isolated on other occasions, but the clinical picture presented by the patients was a febrile disease for no more than five days. The patients recovered without apparent sequelae. Further studies in monkeys must be made, to determine if the concomitant infection is responsible either for an increase in the severity of symptoms or is only related to the strain of *P. falciparum*.

Finally, it is important to remember that the typical periodic fevers associated with both types of malarial parasites are masked by the continuous fever caused in the arbovirus infection.

Treatment implications. Many cases of febrile disease are diagnosed each year and treated as malaria. After treatment some of them continued to have fever and with such cases either the treatment failed or an arbovirus could be associated. In the case of mixed infection of arboviruses and malaria if the fever continues and the blood smears are negative then the specific treatment for malaria should not be repeated, since either fever or other symptoms may be caused by an arbovirus and not malaria, as was seen in the present cases.

In the last instance, without a specific laboratory diagnosis of malaria, it is not advisable to treat patients just because they have fever and live in endemic malarious areas.

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RESUMO: Seis casos nos quais infecções por arbovirus e malaria foram observadas no mesmo e ao mesmo tempo. O diagnostico foi feito por isolamento de virus. Os arbovirus isolados estão incluidos na familia Bunyaviridae, genero *Bunyavirus*. *Plasmodium falciparum* (diagnosticado por gota espessa e esfregaço sanguineo) foi associado com os seguintes arbovirus: Guaroa (grupo California) 3 vezes; Tacaiuma (grupo Anopheles A) 2 vezes e Catu (grupo Guama) uma vez. O último paciente estava também infectado por *P. vivax*.

Dos seis pacientes cinco eram homens e um mulher. Todos apresentavam 17 años de idade ou mais. Embora morassem no Estado do Pará, nenhum nasceu no mesmo. A mulher era domestica, 4 homens trabalhadores rurais e um comerciante ambulante.

A história clínica principal de doença consistiu de febre com cefalea, calefrios, mialgias e artralgias. Em alguns, observouse dor abdominal, náuseas, vômitos e tontura. Icterícia foi registrada em dois casos de *P.*

falciparum em associação com Tacaiuma. A febre era contínua e não periódica, que é típica da malaria. Os pacientes foram tratados pela SUCAM con cloroquina, primaquina, quinino, ou outras drogas, quando necessário. Cinco deles recuperaram sem sequelas e um morreu.

Esses casos são importantes porque na Amazônia milhares de casos são diagnosticados e tratados como malaria. Um número consideravel das cepas de *P. falciparum* são consideradas resistentes aos antimaláricos. A possibilidades (provavelmente subestimada) de infecções concomitantes com arboviroses, pode mascarar ou alterar a eficácia do tratamento ou levar a falsos diagnósticos.

É possível que casos de infecções simultâneas de malaria e Guaroa ou Tacaiuma, sejam devidas, na Amazônia, ao fato de que os vetores em ambos os casos em áreas da floresta, são os mosquitos *Anopheles nuneztovari* e *A. triannulatus*.

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