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IMPACT OF COINFECTION OF PV B19 ON THE COURSE AND PROGNOSIS OF MALARIA CAUSED BY *PLASMODIUM FALCIPARUM*

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Absract. Parvovirus infection (PVI) is widespread in the world; more than 80% of the adult population have antibodies of IgG class to parvovirus B19. Malaria is a vector-borne parasitic disease caused by the protozoa of the genus *Plasmodium*, that is widespread in the countries of Africa, Southeast Asia, Oceania. The objective of the present study was to evaluate the effect of parvovirus B19 infection on the clinical course of malaria and the outcome of the underlying disease. During the period 2016–2018 blood plasma samples of 316 patients from the hospital of the Friya Prefecture of the Republic of Guinea (GR) with confirmed diagnosis of malaria were examined for the presence of PVB19 DNA. The clinical course of malaria in 316 examined patients was divided into group of either mild or complicated. In total, PVB19 DNA was detected in blood plasma in 55 of 316 patients (17.41±2.13%). But in the group with co-infection of PVB19 and *P. falciparum* complications were observed in 40 of 55 (72.73±2.75%) patients, and in 6 of 55 cases (10.91±4.40%) the disease resulted in death. In the group of patients with malaria without PVI, complications occurred in 99 of 261 patients (37.9±3.0%); of those 2 (0.77±0.54%) died. It was found that the most numerous group in the structure of malaria patients is represented by children under 5 (median 3) years (89, or 28.25±2.53%). Our results correlate with the data of other researchers who studied the PVI-associated malaria in children in malaria-endemic regions: among children under 5 years, the absolute majority of cases of PVI was accompanied by a complicated course of malaria. The primary parvovirus infection can aggravate the course of malaria, especially when combined with other unfavorable conditions (iron deficiency, malnutrition, helminthic infections, co-infections, etc.). Thus, infection with PVB19 becomes a critical factor, which can provoke a severe life-threatening anemia, and also cause other complications.

Key words: *parvovirus infection, DNA of parvovirus B19, Plasmodium falciparum, malaria, anemia.*

ВЛИЯНИЕ КОИНФИЦИРОВАНИЯ PVB19 И *PLASMODIUM FALCIPARUM* НА ТЕЧЕНИЕ И ПРОГНОЗ МАЛЯРИИ

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Резюме. Парвовирусная инфекция (ПВИ) широко распространена в мире: более 80% взрослого населения имеют антитела класса G к парвовирусу B19. Малярия — трансмиссивное паразитарное заболевание, вызываемое

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простейшим рода *Plasmodium*, широко распространенное в странах Африки, Юго-Восточной Азии, Океании. Целью работы было изучение влияния инфицирования парвовирусом B19 на клиническое течение малярии и исход основного заболевания. В период 2016–2018 гг. на наличие ДНК PVB19 исследованы образцы плазмы крови больных госпиталя префектуры Фрия Гвинейской Республики (ГР) с лабораторно подтвержденным диагнозом «малярия». Клиническое течение малярии у 316 обследованных пациентов оценивали как «простое» и «осложненное». В целом, ДНК PVB19 DNA была выявлена в плазме крови 55 из 316 пациентов (17,41±2,13%). Но в группе больных с коинфицированием PVB19 и *P. falciparum* осложненное течение малярии наблюдали у 40 из 55 (72,73±2,75%) пациентов, и в 6 из 55 случаев (10,91±4,40%) регистрировали летальный исход. В группе пациентов с малярией без коинфицирования парвовирусом B19 осложнения наблюдались у 99 из 261 пациента (37,9±3,0%); из них 2 (0,77±0,54%) умерли. Было обнаружено, что наиболее многочисленная группа в структуре больных малярией представлена детьми в возрасте до 5 лет (средний 3 года) (89, или 28,25±2,53%). Наши результаты коррелируют с данными других исследователей: среди детей в возрасте до 5 лет, проживающих в районах, эндемичных по малярии, абсолютное большинство случаев парвовирусной инфекции сопровождалось осложненным течением малярии. Парвовирусная инфекция, развивающаяся в раннем детском возрасте, может усугублять течение малярии, особенно на фоне других неблагоприятных условий (дефицит железа, недоедание, гельминтные инвазии, коинфекции и пр.). При этом инфицирование PVB19 становится критическим фактором, который может провоцировать злокачественное течение анемии с угрозой для жизни, а также вызывать другие осложнения.

Ключевые слова: *парвовирусная инфекция, ДНК парвовируса B19, Plasmodium falciparum, малярия, анемия.*

Introduction

Parvovirus infection (PVI) is widespread in the world; more than 80% of the adult population have antibodies of IgG class to parvovirus B19 [6]. The causative agent of PVI is the DNA-containing parvovirus B19 (PVB19). PVB19 has a tropism for cells carrying P-antigen (Gb4 receptor). These are the precursor cells of the erythroid bone marrow lineage, liver, spleen, heart and intestine tissues, mature erythrocytes, granulocytes, endothelial and smooth muscle cells of the vessels. Depending on the hematological and immunological status, the manifestations of PVI vary from asymptomatic course or mild exanthemic disease (infectious erythema) to severe forms (aplastic crisis, pancytopenia, acute hepatitis, fulminant hepatic failure, encephalitis, cardiomyopathy and myocarditis). Parvovirus infection complicates the course of diseases accompanied by immunodeficiencies (oncological, hematological, etc.) [1, 2, 9]. According to several authors, infection with PVB19 can aggravate the course of malaria [3, 8, 12, 14].

Malaria is a vector-borne parasitic disease caused by the protozoa of the genus Plasmodium, that is widespread in the countries of Equatorial Africa, Southeast Asia, Oceania, Central and South America. The problem of malaria is especially urgent for the Sub-Saharan Africa. This territory accounts for 90% of cases and 92% of deaths from malaria in the world. According to WHO, in the Republic of Guinea (GR) in 2015, 811 000 cases of laboratory-confirmed malaria were detected. The disease proceeds with cyclic fever, febrile paroxysms, hepatorenal and anemic syndrome. Severe complications of malaria leading to death can be cerebral edema, cerebral (malarial) coma, splenic and kidney failure, disseminated intravascular coagulation syndrome (DIC-syndrome), acute massive hemolysis, hemoglobinuria, hemorrhagic syndrome.

The objective of the present study was to evaluate the effect of parvovirus B19 infection on the clinical course of malaria and the outcome of the underlying disease.

Materials and methods

During the period 2016–2018 blood plasma samples of 316 patients from the hospital of the Friya Prefecture of the Republic of Guinea (GR) with confirmed diagnosis of malaria were examined for the presence of PVB19 DNA. DNA PVB19 was detected by PCR using the sets of reagents Ampliprime "RIBO-prep" and "AmpliSens® Parvovirus B19-FL" (Central Institution of Epidemiology, Rospotrebnadzor, Russia) in accordance with the manufacturer's instruction.

Statistical treatment of the results was carried out using the analysis of frequency distributions and conjugacy tables using the GraphPadInStat 3 software. The significance of the differences and the confidence interval were determined by the Student's t-test. Differences were considered significant at $p < 0.01$.

Results

The clinical course of malaria in 316 examined patients was divided into group of either mild or complicated. A mild course of malaria was detected in 177 (56.01±2.79%) patients. This form of the disease was characterized by fever with temperature not exceeding 39°C, general weakness and moderate anemia (hemoglobin concentration higher than

Table 1. The effect of parvovirus B19 infecting on the course of malaria in patients of Fria Prefecture of the Republic of Guinea

Course of malaria	Number of patients, abs./%	Presence of PV19 DNA	
		Positive, abs./%	Negative, abs./%
Mild	177/56.01±2.79	15/27.27±2.75	162/62.07±3.0
Complicated	139/43.99±2.79	40/72.73±2.75	99/37.93±3.0
Lethal outcome	8/2.53±0.88	6/10.91±4.40	2/0.77±0.54
Total	316/100	55/17.41±2.13	261/82.6±2.13

70 g/l). 139 patients (43.99±2.79%) manifested the complicated course of malaria that was accompanied by a rise of the temperature up to 40°C, nausea, vomiting, severe anemia (hemoglobin concentration lower than 70 g/l), high levels of transaminases, creatinine, a decrease in the total protein in the blood. In 8 (2.53±0.88%) cases, the severe course of the disease led to a fatal outcome.

Plasma samples of patients with mild and complicated forms of malaria were tested for the presence of PVB19 DNA. The results are shown in Table 1.

In total, PVB19 DNA was detected in blood plasma in 55 of 316 patients (17.41±2.13%). In groups of both PVB19-positive and negative patients, cases of mild and complicated as well as fatal outcomes were detected. However, in the group with co-infection of PVB19 and *P. falciparum*, complications and mortality rates were significantly higher. Indeed, complications were observed in 40 of 55 (72.73±2.75%) patients, and in 6 of 55 cases (10.91±4.40%) the disease resulted in death. In the group of patients with malaria without PVI, complications occurred in 99 of 261 patients (37.9±3.0%); of those 2 (0.77±0.54%) died. Thus, the probability of developing a complicated course of malaria with a co-infection is significantly higher than in the absence of PVI ($p < 0.0001$; RR = 1.917; 95% CI: 1.532 to 2.399).

To study the age structure of patients with malaria, they were distributed into seven age groups: 0–5, 6–10, 11–15, 16–25, 26–45 and 46–65 years old (Table 2). It was found that the most numerous group in the structure of malaria patients is represented by children under 5 (median 3) years (89, or 28.25±2.53%). The lowest number of malaria cases falls into the age group of 46–65 (median 57) years — 17 cases, or 5.4±0.71%. It is noteworthy that the DNA of PVB19 in the blood plasma of patients of this group has not been detected.

In other age groups of patients with malaria, the presence of PVB19 DNA in the blood plasma is characterized by the following rates: among children under 5 years (median 3 years) it was detected in 17.98±4.07% of patients; in the group of 6–10 years (median 8 years), the detection rate increased to 28.85±6.28, and reached a maximum of 34.29±8.02% in the group of 11–15 years (median 13 years). These results indicate a wide prevalence of parvovirus infection among children and adolescents and correspond to the data available in the literature [5, 13, 15]. In older patients, this value was reduced to 15.38±5.0% in the group of 16–25 years (median 20 years), to 5.71±3.22% in the group of 26–45 years (median 36.5 years) and zero in the age group of 46–65 years (median 57 years). The severity of PVB19-associated malaria was analyzed in different age groups. The results are summarized in Table 3.

As can be seen from the results presented, the maximum number of cases of complicated malaria with PVI (n = 15) was observed in patients under 5 years old, where it accounts for 93.75±6.05% of cases comparing to 27.27±7.04% among all PVB19-positive patients. The likelihood of developing a complicated course of malaria with a co-infection in this age group is significantly higher than in the absence of PVI ($p = 0.0001$; RR = 2.44; 95% CI: 1.780–3.357). It is important to note that 6 out of 8 deaths occur in this group, that is significantly higher than in the absence of infection with PV B19 ($p = 0.0003$, RR = 13.688, 95% CI: 3.034–61.740). With age increase, the incidence of complicated course of PVI-combined malaria decreases, although the trend persists in individuals under 26 years of age. Thus, among patients of 6–10 years of age, complicated malaria was recorded in 18.18±5.75% of PV B19-infected persons; in the group of 11–15 years — in 14.55±5.14% of cases; in persons from 16 to 25 years in 9.09±4.07% of cases. However, the differences in the course of malaria between patients infected and not infected with parvovirus B19 are not statistically reliable in all these age groups.

Table 2. Age distribution of malaria patients with combined parvoviral infection

Age group, years	Number of patients, abs./%	PVB19-positive, abs./%
0–5	89/28.25±2.53	16/17.98±4.07
6–10	52/16.51±2.09	15/28.85±6.28
11–15	35/11.11±1.77	12/34.29±8.02
16–25	52/16.51±2.09	8/15.38±5.00
26–45	70/22.22±1.16	4/5.71±3.22
46–65	17/5.40±0.71	0/0.0
Total	315/100	55/17.46±2.14

Table 3. Mild and complicated course of malaria associated with parvovirus B19 infection in different age groups

Age, years	Mild disease, abs./%	Complicated disease, abs./%
0–5	1/1.82±1.80	15/27.27±7.04
6–10	5/9.09±3.88	10/18.18±5.75
11–15	4/7.27±3.50	8/14.55±5.14
16–25	3/5.45±3.06	5/9.09±4.07
26–45	2/3.64±2.52	2/3.64±2.57
46–65	0/0.0%	0/0.0%
Total (n = 55)	15/27.27±6.01%	40/72.73±11.50%

Discussion

It is known that in seronegative individuals with primary infection parvovirus in the acute phase can cause a failure of erythrocytes formation for up to 5–7 days, which leads to a significant decrease in hemoglobin [15]. Erythrocytes are also the main target of the malarial plasmodium, which multiplies within and destroys them thus causing anemia of varying severity. According to several authors, infection with PVI occurs after decrease in cellular immunity caused by *P. falciparum* [4, 7]. There is evidence that in severe malaria-endemic regions severe forms of anemia are the main cause of child mortality. Thus, severe anemia is considered the cause of childhood death in malaria in 17–54% of cases [11, 13].

Our results correlate with the data of other researchers who studied the PVI-associated malaria in children in malaria-endemic regions: among children under 5 years, the absolute majority of cases of PVI was accompanied by a complicated course of malaria [4, 10, 14].

Having in mind that according to studies, in African countries 50 to 90% of the population by age 6 have IgG antibodies to PVB19 [15] and, based on the results obtained, it can be assumed that the probability of complicated course of PVI-associated malaria depends on the age of the patient. The older the patient, the higher the probability of having immunity to parvovirus, and, therefore, the less influence the associated infection demonstrates.

In contrast, the primary parvovirus infection, which normally occurs in early childhood, is acute and can aggravate the course of malaria, especially when combined with other unfavorable conditions (iron deficiency, malnutrition, helminthic infections, co-infections, etc.). Thus, infection with PVB19 becomes a critical factor, which can provoke a severe life-threatening anemia, and also cause other complications.

In general, the results of this study indicate a high medical-social significance of parvovirus infection for countries endemic for malaria.

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