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MALARIA: THE FORGOTTEN THREAT. A CASE STUDY OF PATIENTS HOSPITALIZED IN THE DEPARTMENT OF INFECTIOUS DISEASES AND HEPATOLOGY AT THE POMERANIAN MEDICAL UNIVERSITY SZCZECIN

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Abstract. Malaria remains a major health issue In the world, while in Poland no cases of the indigenous disease have been observed since 60-ties of the last century, but the number of cases imported from the epidemic areas is increasing. The aim of work was to analyse the epidemiology of malaria diagnosed and treated in the Department of Infectious Diseases and Hepatology, Pomeranian Medical University, Szczecin, Poland from 1.02.2010 until 31.01.2011. In total 11 cases were found, all diagnoses based on the thick and thin blood smear microscopy, alongside to the standard laboratory analyses. All clinical data presented are based on the case history. Results: Majoriry of cases reported travel to Sub-Saharan Africa (45%) or Indian subcontinent (27%). The travel was usually for recreational purposes, with significant proportion (45%) of patient not taking the malaria prophylaxis. Clinical course of infections was largely mild, with dominance of *Pl. Falciparum* parasitaemia. Fever was the most common clinical symptom (90%), while in the routine laboratory test no significant abnormalities, suggesting the disease, were found. Conclusions: malaria should be suspected in every case of the returning traveler with fever, especially if the travel was to the endemic area. The exclusion of the disease cannot be based on routine laboratory tests or quick immunoassays – thick and thin blood smear microscopy must be performed.

Keywords: clinical features, Malaria, *Palsmodium* spp.

INTRODUCTION

In recent years, owing to an upward trend in tourism rates, the endemic areas of tropical diseases have become a popular destination for both leisure and business activities among Poles [Paul and Stefaniak 2007, ECDC 2010]. On the other hand, the number of

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medical consultations concerning risk evaluation and chemoprophylaxis regimens for individuals visiting these regions has remained stable. This has lead to a situation where most travelers rely their safety on second-hand information from tourist offices or employer representatives rather than qualified medical personnel [Paul and Stefaniak 2007].

In tropical regions, malaria is the most common infectious disease, affecting both local communities as well as foreign visitors. Although among indigenous population, due to stable transmission, the infection rarely proves severe or lethal, in can become a serious issue for foreigners. The lack of innate immune system mechanisms and specific antibodies results in a more rapid disease progression and is associated with considerable mortality [Hay et al. 2004, Snow et al. 2005].

Owing to the fact that Szczecin is not only a seaport, but is also situated in the vicinity of German border, people travelling back from the tropics have always received meticulous medical attention. In the past, the number of patients hospitalized with malaria was substantially higher than the rates for other centers. Additionally, the Department of Infectious Diseases and Hepatology at the Pomeranian Medical University is the only place in the West Pomeranian Voivodeship region, where thorough *Plasmodium* infection diagnostics, including molecular biology testing, is available. Apart from chloroquine, a drug of marginal importance in malaria treatment, the access to antimalarial medications in this region is much limited. Other drugs are only available in two centers – Koszalin and Wałcz. This contributes to the role of our Department in malaria management.

The aim of this study was the epidemiological analysis of all confirmed malaria cases hospitalized in Department of Infectious Diseases and Hepatology at the Pomeranian Medical University, Szczecin, between 2nd February 2010 and 31st January 2011.

MATERIAL AND METHODS

Eleven patients (seven females) with confirmed malaria, hospitalized in the Department of Infectious Diseases and Hepatology between February 2nd 2010 and January 31st 2011, were included in this study. Subjects were aged between 26 and 61. In all patients malaria was diagnosed by the presence of parasites in both thick and thin peripheral-blood smears. The latter test allowed the *Plasmodium* species detection and parasitemia calculation. All subjects were interviewed concerning their destination, length of stay, trip purpose, type of chemoprophylaxis administered and period between first symptoms and diagnosis. Physical examination revealed main signs and symptoms in the studied group. In all individuals, peripheral blood parameters, including cell morphology, inflammatory indicators, liver and renal profiles, total serum protein and blood glucose levels, were measured. More detailed information is presented in Table 1. Rapid antigen immunoenzymatic assay for both *Plasmodium* spp. and *Plasmodium falciparum* identification was employed in all patients. The blood examination was performed in the Department's laboratory.

Table 1. Peripheral blood parameters and reference ranges
Tabela 1. Parametry krwi obwodowej i zakresy referencyjne

Test Badanie	Norm Norma	Test Badanie	Norm Norma
Blood count – ERY Morfologia – ERY	3.90–5.70 · 10^{-6}	INR	0.8–1.2
Blood count – HGB Morfologia – HGB	12.0–17.0 g · dl^{-1}	D-dimery	<500 ug · l^{-1}
Blood count – WBC Morfologia – PLT	4.00–10.00 · 10^{-3}	fibrinogen fibrynogen	1.8–3.5 g · dl^{-1}
Blood count – PLT Morfologia – PLT	150–400 · 10^{-3}	creatinine kreatynina	0.50 – 1.20 mg · dl^{-1}
CRP	<5.0 mg · dl^{-1}	Na^+	136.0 – 145.0 mmol · l^{-1}
Procalcitonin	<0.50 mg · dl^{-1}	K^+	3.7 – 5.5 mmol · l^{-1}
AST	<40 IU · ml^{-1}	fasting blood glucose level glikemia na czczo	70–105 mg · dl^{-1}
ALT	<41 IU · ml^{-1}	TP	6.6 – 8.7 g · dl^{-1}
Total bilirubin	0.0–1.2 mg · dl^{-1}	ALB	4.02 – 4.76 g · dl^{-1}

Blood count – ERY – erythrocytes; Blood count – HGB – hemoglobin; Blood count – WBC – white blood cells; Blood count – PLT – plates counts; CRP – C-reactive proteine; AST – asparate aminotransferase; ALT – alanine aminotransferase; TP – Total protein; ALB – albumin. Morfologia – ERY – erytrocyty; Morfologia – HGB – hemoglobina; Morfologia – WBC-leukocyty; Morfologia – PLT – płytki krwi; CRP – białko C-reaktywne; AST – aminotransferaza asparaginianowa; ALT – aminotransferaza alaninowa; INR – znormalizowany czas protrombinowy; TP – białko całkowite; ALB – albuminy.

RESULTS AND DISCUSSION

Almost a half of patients suffering from malaria went to Sub-Saharan Africa (45.5%), compared to 27.3% who chose India or Sri Lanka for their destination. Syria, South-East Asia and Mexico were less popular and were visited by only one patient, each (Fig. 1). Women travelled to malaria endemic regions for leisure. In contrast, three of four men indicated work as their trip purpose (all of them are seamen). Among those who visited the tropics recreationally, the length of stay exceeded two weeks in only two instances, whereas all workers remained there for over a month.

Out of eleven patients, as few as three received antimalarial prophylaxis, however, in only two cases atovaquone/proguanil was dosed adequately. It should also be stressed that the most severe form of malaria developed in patient who had received prophylaxis from his employer and stayed in a malaria-endemic country for more than one month.

In most cases, disease symptoms occurred within 2–3 days from return (45.4%). The period reached 14 days in 27.3% of patients, exceeding 30 days in two instances of *Plasmodium falciparum* infection. These patients received antibiotics with antimalarial activity due to the presence of non-specific infection symptoms. Fever was the single most prevalent symptom affecting nearly all patients (90.1%). In four cases (36.4%) the clini-

cal manifestations were non-specific, suggesting pulmonary or gastrointestinal tract involvement. Multiple organ disfunction syndrome with disseminated intravascular coagulation, neurological deficits and renal failure was observed in one case.

Fig. 1. World regions visited by patients who contracted malaria*
Rys. 1. Regiony świata, z którego powrócili pacjenci z malarią*

* Two patients who returned from Sub-Saharan Africa were not able to specify their destination.
* Na rysunku nie przedstawiono dwóch pacjentów, którzy powrócili z rejonu Afryki Subsaharyjskiej bez możliwości sprecyzowania konkretnego miejsca.

Parasitological testing, comprising thin and thick blood smears, demonstrated *Plasmodium falciparum* infection in 54.5% of subjects. *Plasmodium* vivax was recognized in two and ovale in one case. Despite the use of ELISA serological test, performed in Institute of Marine and Tropical Medicine, Gdynia, we failed to correctly identify *Plasmodium* species in blood samples from one of the patients. Parasitemia level did not exceed 3‰ in 10 *Plasmodium* infected patients, spiking to 8% in the most severe case. Positive result of rapid immunoeznymatic assay for *Plasmodium* detection served as an additional confirmation of this score. For diagnosis of malaria, there are no laboratory tests to replace microscopic blood evaluation, which is being currently recommended by World Health Organization. In three patients a slightly raised leukocyte count was the only hematologic abnormality. In case of the aforementioned patient with multiple organ disorder syndrome, laboratory tests revealed thrombocytopenia. Anemia followed during treatment.

With regard to inflammatory parameters, increased procalcitonin value was only seen in the case of severe malaria. On the other hand, C-reactive protein was above normal levels in 8 patients, ranging from 5.8 to 270 mg · ml^{-1}. Nevertheless, it was not possible to

differentiate between infection-induced inflammation and bacterial superinfection. Surprisingly, although an increase in aminotransferase activity is to be expected, owing to liver cell damage typically associated with *plasmodium* life cycle, in this study group it proved relatively rare. Aspartate and alanine aminotransferase activities were increased in 2 and 4 instances, respectively. Hyperbilirubinemia, commonly associated with either liver damage or hemolysis, was detected in only three cases, resulting in clinical jaundice in only one patient. Coagulopathy with disseminated intravenous coagulation and was only observed in the instance of severe malaria and no blood clotting disorders were present in the rest of the group. Interestingly, an increase in either fibrinogen levels or fibrinogen degradation products were seen in the majority of patients (54.3 and 63.7%). With the exception of the severe malaria case, where blackwater fever developed, no signs of renal impairment, i.e. elevated serum creatinine or electrolyte disturbance were noted. Apart from the instances of diabetic patients, fasting glycaemia in the studied group was within norm. Total protein and albumin concentrations remained unchanged, but the latter was notably low in three cases. Table 2 gives more information on laboratory tests results.

Table 2. Mean values of laboratory parameters
Tabela 2. Średnie wartości badanych parametrów laboratoryjnych

	ERY	HGB	WBC	PLT	CPR	Prokalcytonina	AST	ALT	bili
Average Średnia	4.61	13.44	8.19	255.64	83.64	0.51	66.64	64.82	0.83
SD	0.48	1.11	4.15	114.37	–*	–*	–*	–*	0.69
MIN	3.85	12.10	3.71	51.00	0.81	0.05	19.00	17.00	0.17
MAX	5.41	15.70	15.18	466.00	270.96	1.85	403.00	227.00	1.96
	INR	d-dimery	fibryn.	kreatynina	Na	K	glikemia	TP	ALB
Average Średnia	0.95	4476.70	5.06	1.17	136.30	4.09	108.82	14.71	3.81
SD	0.23	–*	1.62	–*	4.69	0.31	28.09	–*	0.58
MIN	0.40	296.00	3.30	0.59	124.00	3.30	85.00	6.00	3.00
MAX	1.30	32372.00	8.00	5.37	140.80	4.40	177.00	76.00	4.64

SD – standard deviation; MIN – minimal value; MAX – maximal value.
* – parameter not in normal distribution.
SD – odchylenie standardowe; MIN – wartość minimalna; MAX – wartość maksymalna.
* – parametr nie spełnia rozkładu normalnego.

Since the sixties of the twentieth century there have been no malaria-endemic regions in Europe. Although malaria presented a serious issue in the beginning of the twenties (a few thousand cases were registered in 1921) – [Dzbeński 2008] as well as shortly after the Second World War (nearly ten thousand instances in 1948), the disease has been successfully eradicated and the last malaria case was observed in 1963 [Lonc and Płonka-Syroka 2004, Brzeziński 2005, Dzbeński 2008]. Since then malaria has become an imported disease. The introduction of antimalarial prophylaxis and severe restrictions in international travel during the Communist Era in Poland resulted in a sharp decline in the inci-

dence rates to approximately 20 new cases annually [Lonc and Płonka-Syroka 2004]. The figures have risen markedly since the second half of 1990's when tourism industry and labor migration were finally established. This trend is evident in the studied group, with men travelling for work and women for recreational purposes [Paul and Stefaniak 2007, Kotłowski 2007].

WHO also recommends a special focus on malaria prevention and control by means of mosquito avoidance measures, such as protective clothing, insect repellents and appropriate prophylactic drug regimens [Kotłowski 2007, ECDC 2010], which should depend on the trip purpose and the length of the stay in malaria endemic regions. Only one of eleven subjects consulted a specialist before travelling. The vast majority of patients did not receive any prophylactic medications and the fact that the patient suffering from the most severe form of malaria did deserves attention.

CONCLUSIONS

Recently, a belief that a negative result of a rapid immunoeznymatic assay is sufficient for ruling out *Plasmodium* infection has been prevalent among emergency department workers. WHO, on the other hand, points out the low sensitivity of this test and recommends the use classical diagnostic tools, i. e. thin and thick blood films. Quick tests should solely be used for screening purposes. In this study there was only one instance of a positive rapid test result and this was the case in severe malaria. The test was negative in all other patients [Müklberger et al. 2003]. What is more, most patients did not show any specific changes in blood test results, and it was the medical interview together with clinical symptoms that made the diagnosis possible.

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MALARIA – ZAPOMNIANE ZAGROŻENIE, ANALIZA PRZYPADKÓW MALARII U OSÓB LECZONYCH W KLINICE CHORÓB ZAKAŹNYCH I HEPATOLOGII POMORSKIEGO UNIWERSYTETU MEDYCZNEGO W SZCZECINIE

Streszczenie. Malaria ciągle jest głównym problemem zdrowotnym świata, natomiast w Polsce od lat 60. ubiegłego wieku nie stwierdzono rodzimych przypadków malarii. Zwraca jednak uwagę ostatnio rosnąca liczba pacjentów z malarią powracających ze stref epidemicznych. Celem pracy była analiza epidemiologiczna wszystkich przypadków potwierdzonej malarii leczonych w Katedrze i Klinice Chorób Zakaźnych PUM w Szczecinie w okresie między 1.02.2010 a 31.01.2011 r. Do analizy zakwalifikowano 11 przypadków malarii hospitalizowanych w Oddziale Chorób Zakaźnych i Hepatologii. U wszystkich rozpoznanie tej parazytozy oparto na badaniu grubej kropli i cienkiego rozmazu, dodatkowo u wszystkich wykonano rutynową diagnostykę laboratoryjną. Dodatkowe informacje uzyskano na podstawie poszerzonego wywiadu lekarskiego. Wyniki: najczęściej pacjenci z malarią powracali z Afryki Subsaharyjskiej (45%) bądź z Półwyspu Indyjskiego (27%). Większość osób wyjeżdżała w celach turystycznych, a znamienna większość nie przyjmowała chemoprofilaktyki przeciwmalarycznej. Wśród analizowanych pacjentów, poza jednym przypadkiem, dominowały łagodne postaci malarii, głównie gatunek *Pl. falciparum*. Prawie u wszystkich osób występowała gorączka (90%), natomiast w rutynowych badaniach dodatkowych nie wykazano odchyleń uznanych za wykładniki tej choroby. Wnioski: malarię należy podejrzewać u każdego chorego powracającego z rejonu epidemicznego, zwłaszcza, jeżeli występuje gorączka. Nie można wykluczyć tej choroby na badaniach rutynowych czy szybkich testach immunoenzymatycznych, a jedynie na podstawie grubej kropli i cienkiego rozmazu.

Słowa kluczowe: cechy kliniczne, malaria, *Plasmlodium* spp.

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