PROBLEMS OF EARLY MALARIA DIAGNOSTICS IN NON-ENDEMIC COUNTRIES

Kozko V.
Doctor of medical science, Professor,
Head of the Department of Infectious Diseases of Kharkiv National Medical University, Ukraine
Mohylenets O.
PhD, Assotiate professor of the Department of Infectious Diseases of Kharkiv National Medical Uiversity, Ukraine
Makhmudov Yu.
Student of the 6th course of Kharkiv National Medical University, Ukraine
Merkulova N.
PhD, Assotiate professor of the Department of Infectious Diseases of Kharkiv National Medical University, Ukraine
Yekimova N.
Head of the Diagnostics Department of Kharkiv Regional Clinical Infectious Diseases Hospital, Ukraine

Abstract
Analysis of clinical and epidemiolodical features of malaria in Kharkiv region was perfomed. Main reasons of malaria misdiagnosis on early terms of the disease were revealed. Practical recommendations were done.

Keywords: malaria, non-endemic countries, clinic, epidemiology, diagnostics, misdiagnosis reasons.

Malaria is considered to be one of the most up-to-date and widespread problems of the mankind. According to the World Health Organization (WHO), about 3,2 billion people in 106 countries are under the threat of malaria. According to WHO' s data, in 2016, there were 216 million cases of malaria registered in the world. The presence of the disease was detected in 91 countries, 80% of cases of malaria occurred in 15 countries, 90% – in the African region of the WHO [1].

All registered cases of malaria in Ukraine, which is non-endemic country, are imported (foreign students, travelers, etc.). High levels of the population migration, global climate changes can lead to spreading of malaria beyond it habitual existence [2, 3].

The low awareness and alertness of doctors about malaria is a significant problem. It is wel-known fact that rare diseases are difficult to diagnose. Baesides, sometimes patients for different reasons hide the fact of being in endemic countries, which also considerably complicates the diagnostic search [2, 3].

The purpose of the work is to improve the early malaria diagnostics in non-endemic countries on the basis of the study of clinical, anamnestic and epidemiological data.

Tasks:

1. To study the etiological and epidemiological features of imported malaria in the Kharkiv region.
2. To study the clinical features of the malaria in the first days of the disease.
3. To identify the most common reasons of misdiagnosis and give practical recommendations.

Materials and methods. The research was carried out at the Department of Infectious Diseases of Kharkiv National Medical University, which based on Kharkiv Regional Clinical Infectious Diseases Hospital (KhRCIDH).

34 archival case histories of patients with malaria who received treatment at KhRCIDH in 2011-2017 were analyzed.

The diagnosis was established on the basis of clinical and epidemiological data and in all cases confirmed by parasitoscopy (thin and thick smear, staining by Romanovsky-Gimza).

The statistical analysis of the obtained data was carried out by the method of variation statistics using Student's T-test and Pearson chi-squared test ($\chi 2$). The calculations were performed on IBM PC using Excel spreadsheets. Differences were considered as significant at $p<0,5$.

Results. Among hospitalized patients were predominantly men – 31 (91,1%).

The age of the patients varied from 18 to 72 y.o. and on average was 29,34±2,36 y.o. Half of the patients (17 people) were younger than 25 y.o., mostly they were students of Kharkiv universities. 38% of patients belonged to the age group of 25-44 years. So, according to the WHO age classification, the vast majority of patients (88%) belonged to the youth/young age group.

In 2011 9 cases of imported malaria were confirmed, in 2012 – 6, in 2013 – 4, in 2014 – 5, in 2015 – 3, in 2016 – 3, in 2017 – 4.

Among the patients there were 9 (26,47%) Ukrainians and 25 (73,53%) foreigners.

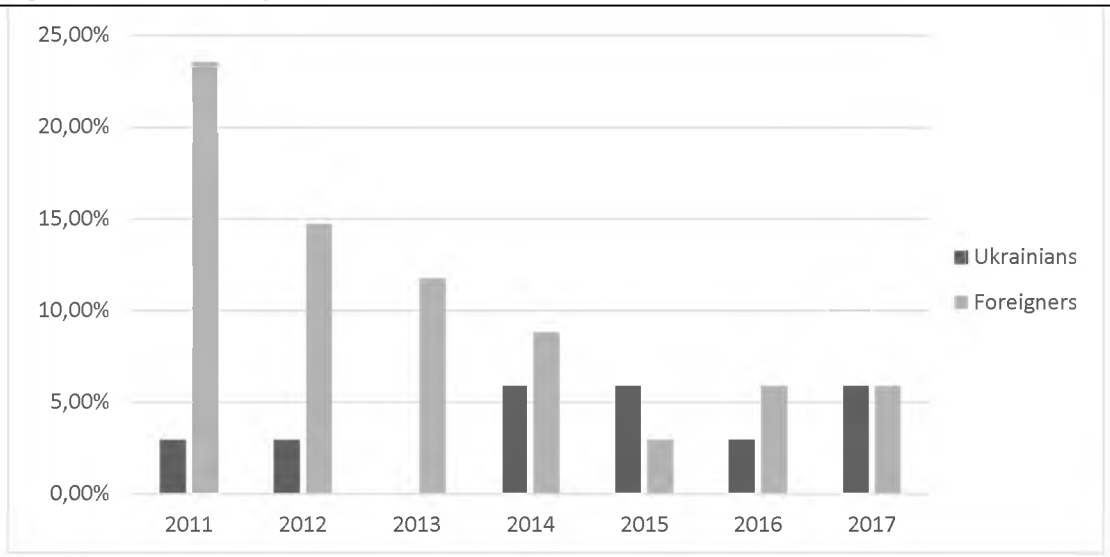

Fig. 1 Distribution of hospitalized patients by origin, %

Comparative analysis of the annual malaria incidence among Ukrainian citizens and foreigners has shown that despite the prevalence of foreigners in the total number of malaria cases, there is a tendency to increase of Ukrainian citizens percentage in the proportion (Fig. 1) that increase importance of the problem. There is a well-known algorithm of examination of foreigners with a fever in Ukraine: parasitoscopy for malaria is obligatory, while for Ukrainians, if there is no data of being in endemic countries (or not collected), such research is not prescribed.

The predominant pathogen in the etiological structure of malaria was *P. falciparum* which was detected in 21 (61,76%) patients as a monoinfection. Moreover, in 4 (11,76%) cases, combination of *P. falciparum* and *P. vivax* was revealed as a mixed infection, in 1 (2,94%) – *P. falciparum* and *P. ovale*. Thus, in general, *P. falciparum* was detected in 26 (76,47%) patients. Other types of plasmodia were less common. Thus, *P. vivax* caused the disease in 4 (11,76%) patients, *P. ovale* – in 3 (8,82%) patients, and in 1 patient there was a mixed infection caused by *P. vivax* and *P. ovale*.

Comparing the etiological structure of malaria among Ukrainians and foreigners, the same tendency was observed – prevalence of *P. falciparum*. The difference between the frequency of detecting of certain causative agents in Ukrainians and foreigners was insignificant (p>0,05).

As it can be seen from Table 1, the vast majority of cases of imported malaria cases (85,29%) related to visit to African countries.

Table 1

Countries where malaria was brought from (abs., %)

N	Country	Part of the world	Number of cases, abs.	Number of cases,%
1	Mali	Africa	1	2,94
2	Nigeria	Africa	8	23,53
3	Congo	Africa	3	8,82
4	India	Asia	2	5,88
5	Liberia	Africa	1	2,94
6	Ghana	Africa	5	14,71
7	Yemen	Asia	1	2,94
8	Cameroon	Africa	7	20,59
9	Afghanistan	Asia	2	5,88
10	Angola	Africa	1	2,94
11	Equatorial Guinea	Africa	1	2,94
12	Cote d'Ivoire	Africa	2	5,88
	Total		34	100,00

The connection between malaria etiology and the history of visiting endemic countries is represented in Table 2.

Table 2

The connection between the etiological structure of malaria and countries, where disease was brought from

Country	Pathogen
Mali	*P. falciparum*
Nigeria	*P. falciparum*
Congo	*P. falciparum, P. vivax*
India	*P. falciparum + P. vivax*
Liberia	*P. falciparum*
Ghana	*P. falciparum, vivax*
Yemen	*P. falciparum + P. vivax*
Cameroon	*P. falciparum +P. ovale, P. falciparum + P. vivax, P. falciparum, P. ovale*
Afghanistan	*P. vivax*
Angola	*P. falciparum*
Equatorial Guinea	*P. ovale + P. vivax*
Cote d'Ivoire	*P. falciparum*

It was found that *P. falciparum*-malaria occurred after visiting all 12 countries mentioned above (Table 2). *P. vivax*-malaria resulted from visiting African (Congo, Ghana, Cameroon, Equatorial Guinea) and Asian (India, Yemen, Afghanistan) countries; *P. ovale* – Cameroon and Equatorial Guinea (West Africa).

Analysis of malaria monthly incidence in 2011-2017 has shown that malaria cases were sporadic. Patients hospitalization took place all over the year, more often in February, September and October, but the difference was insignificant ($p>0,05$), so there was no seasonality.

In average, patients with malaria applied for medical help on 3,06 ± 0,52 day, came to infectious hospital – on 4,42 ± 0,76 day of the disease. Only 17 (50%) patients were hospitalized in the first 3 days of the disease. Reasons of the late (after 3 days) hospitalization were: late appeal for medical help (11 cases) or absence of offers for hospitalization from doctors (6 cases).

It was known from the anamnesis morbi that the first signs of disease appeared in the period from 2 to 390 days after returning from endemic countries (in average duration of presumed incubation period was 100,6 ± 17,5 days). It was more than 1 month in 20 (58,82%) patients, more than 6 months – in 5 people (14,71%), more than 1 year – in 1 person (2,94%), whereas it typically lasts 2-3 weeks.

Description and incidence of the main clinical symptoms in the first day of the disease is represented in Fig. 2.

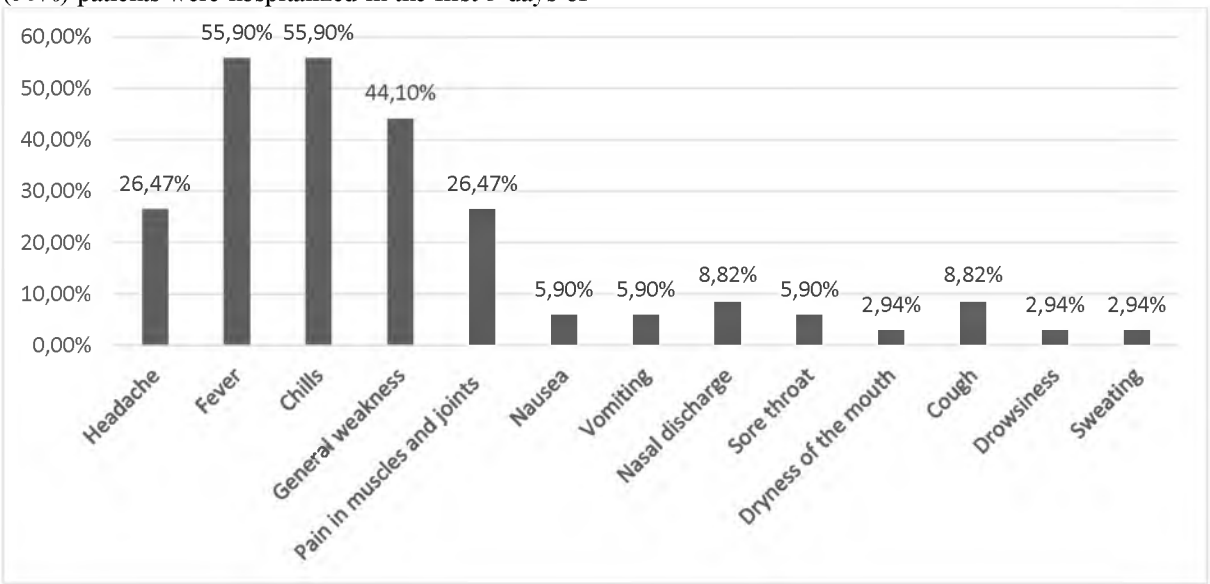

Fig. 2 Incidence of the main clinical symptoms in the first day of the disease, %

The most common first symptoms of the disease were fever and chills, which were observed in 19 (55,88%) patients. It should be noted that other 15 patients did not measure body temperature in the first day of the disease. Sweating, which is the third most common symptom of malaria attack, was noticed only by 1 (2,94%) patient, although we should take into account the fact that not all patients were asked about the presence of this symptom. General weakness was observed in 15 (44,12%), headache and pain in muscles and joints – in 9 (26,47%) patients. Some of patients had symptoms of respiratory or gastrointestinal syndromes (Fig. 2).

At the day of admission also there were symptoms

of intoxication (Table 3), which has considerably grown (fever was observed in 85,30% of patients, in 13 (38,24%) – higher than 39°C). But intermittent fever, which is typical for malaria, was detected only in 11 (32,35%) patients.

Table 3

Incidence of the main clinical symptoms at the day of admission (abs., %)

N	Symptom	Number of cases, abs.	Number of cases,%
1.	Headache	15	44,12
2.	Fever	29	85,30
3.	Chills	15	44,12
4.	General weakness	19	55,88
5.	Pain in muscles and joints	12	35,30
6.	Nausea	8	23,53
7.	Vomiting	6	17,65
8.	Running nose	5	14,71
9.	Sore throat	6	17,65
10.	Dryness of the mouth	7	20,60
11.	Cough	6	17,65
12.	Feeling of heaviness in epigastric region	3	8,82
13.	Pain in eyeballs	3	8,82
14.	Anorexia	4	11,76
15.	Sweating	4	11,76
16.	Loose feaces	3	8,82

Some patients still had symptoms of respiratory and gastrointestinal syndromes (table. 3).

These clinical features probably resulted from prevalence of *P. falciparum* in the ethiological structure.

In the pre-hospital stage malaria was diagnosed only in 49% of patients. In 32% cases acute respiratory infection (ARI) was suspected, in 13% – fever of unknown origin (FUO), in 3% – gastroenteritis, in 3% – meningitis.

At admission department the percentage of misdiagnosis decreased up to 29,41%. Malaria was recognized in 24 patients (70,59%); 7 patients (20,59%) were by mistake diagnosed with ARI, 2 (5,88%) – with FUO, 1 (2,94%) – with meningitis.

Considering first symptoms were nonspecific, it could be one of the reasons of misdiagnosis.

Among other most common reasons of the diagnostics difficulties should be noted poorly collected epidemiological anamnesis – in 17 patients (50%), and language barrier – in 8 (23,53%) patients.

Obtained data coincide with information of scientists from orher non-endemic areas, who also described problems of malaria hypodiagnostics [4-7].

Conclusions.

1. The most common etiological factor of imported malaria was *P. falciparum* which is the most dangerous among malaria pathogens.

2. Mainly malaria was imported from African countries.

3. Despite the prevalence of foreigners in the total number of malaria cases, there is a tendency to increase of Ukrainian citizens percentage in the proportion that increase importance of the problem.

4. The most common reasons of malaria misdiagnosis were poorly collected epidemiological anamnesis, lack of specificity or atypicality of clinical picture of disease, long duration of incubation period and language barrier.

Practical recommendations.

1. Awareness of doctors about malaria in non-endemic countries should be increased. It is strongly recommended to include in the questioning list for medical examination of the patients with fever the question about visiting countries which is endemic to malaria.

2. Not only chemoprophylaxis should be recommended for travelers to endemic countries, but also information about possibility of malaria emergence even after returning into Ukraine should be given. In case of appearance of fever patient should immediately appeal for medical care and inform a doctor about visiting malaria-endemic countries.

REFERENCES:

1. World Health Organization. World malaria report 2017 / World Health Organization. – 2017. http://apps.who.int/iris/bitstream/10665/259492/1/9789241565523-eng.pdf.

2. Trichleb V. I. Laboratorniye pokasateli u bolnich malariyey / Vladimir Ivanovich Trichleb. // Vestnik Vitebskogo gosudarstvennogo meditsinskogo universiteta. – 2013. – N3. – S. 95-105.

3. Golubovska O. A. Malaria: monographia / O. A. Golubovska, A. V. Schkurba, L. A. Kolos. – Kyiv: VSV "Meditsina", 2015. – 288 s.

4. Malaria or flu? A case report of misdiagnosis / [S. Mahdavi, A. Raeesi, L. Faraji et al.] // Asian Pacific Journal of Tropical Biomedicine. – 2014. https://www.sciencedirect.com/science/article/pii/S2221169115302434?via%3Dihub.

5. Higher Rates of Misdiagnosis in Pediatric Patients Versus Adults Hospitalized With Imported Malaria / [A. E. Goldman-Yassen, V. K. Mony, P. M. Arguin et al.] // Pediatric Emergency Care. – 2016. https://journals.lww.com/pec-

online/Fulltext/2016/04000/Higher_Rates_of_Misdiagnosis_in_Pediatric_Patients.5.aspx.

6. Hänscheid T. Current strategies to avoid misdiagnosis of malaria / Hänscheid // Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. – 2003. http://www.biomedsearch.com/nih/Current-strategies-to-avoid-misdiagnosis/12848724.html.

7. Misdiagnosis of cerebral malaria initially as acute psychotic disorder and later as human rabies: a case report / M. H. Mudiyanselage, N. P. Weerasinghe, K. Pathirana, H. Dias // BMC Research Notes. – 2016. https://bmcresnotes.biomedcentral.com/articles/10.1186/s13104-016-2211-3.

EFFECT OF DYSFUNCTION OF THE BLOOD-BRAIN BARRIER, METABOLIC AND ENDOCRINE DISORDERS ON THE DAMAGE OF THE CNS CELLS IN ACUTE VIRUS MENINGITIS AND MENINGOENCEPHALITIS IN ADULTS

Sokhan A.
Ph.D, associate professor,
Infectious diseases department of Kharkiv national medical university

ВЛИЯНИЕ НАРУШЕНИЯ ФУНКЦИИ ГЕМАТОЭНЦЕФАЛИЧЕСКОГО БАРЬЕРА, МЕТАБОЛИЧЕСКИХ И ЭНДОКРИННЫХ РАССТРОЙСТВ НА ПОРАЖЕНИЕ КЛЕТОК ЦНС ПРИ ОСТРЫХ ГЕРПЕСВИРУСНЫХ МЕНИНГИТАХ И МЕНИНГОЭНЦЕФАЛИТАХ У ВЗРОСЛЫХ

Сохань А.
к. м. н., доцент кафедры инфекционных болезней
Харьковского национального медицинского университета

Abstract

68 patients with herpes virus meningitis / meningoencephalitis were examined, among them - 20 with HSV 1, 2 type etiology of neuroinfection, 19 with EBV, 15 with VZV, 14 - HHV-6 with the etiology of meningitis / meningoencephalitis. On the first day of admission to the hospital, levels of lactate, lactate dehydrogenase, cholinesterase, creatine kinase, albumin acid phosphatase, adrenocorticotropic hormone, aldosterone, TSH, T3, T4, and neurospecific markers were determined in patients with CSF patients: NSE, S-100, FRT, F3, TFG, T3, T4, and neurospecific markers: NSE, S-100, FRT The obtained data were analyzed using correlation structures. The effect of dysfunction of the BBB, metabolic and endocrine disorders on the damage of neurons, neuroglia and myelin nerves was determined.

Аннотация

Были обследованы 68 пациентов с герпес вирусными менингитами/менингоэнцефалитами, среди них - 20 с ВПГ 1, 2 типа этиологией нейроинфекции, 19 с ЭБВ, 15 с ВЗВ, 14 – ВГЧ-6 этиологией менингита/менингоэнцефалита. В первые сутки поступления в стационар в ЦСЖ больных определялись уровни лактата, лактатдегидрогеназы, холинэстеразы, креатинкиназы, кислой фосфатазы альбумина, адренокортикотропного гормона, альдостерона, ТТГ, Т3, Т4, и нейроспецифических маркеров: NSE, S-100, GFAP, MBP, BDNF. С помощью построения корреляционных матриц определено влияние нарушения функции ГЕБ, метаболических и эндокринных расстройств на поражение нейронов, нейроглии и миелиновых нервов.

Keywords: herpesvirus meningitis, herpesvirus meningoencephalitis, CSF, neurospecific markers, blood-brain barrier, pathogenesis.

Ключевые слова: герпес вирусный менингит, герпес вирусный менингоэнцефалит, ЦСЖ, нейроспецифические маркеры, ГЭБ, патогенез.

Инфекции ЦНС представляют собой уникальную проблему для врачей благодаря быстрому прогрессу болезни, часто тяжелым течением, высоким процентом летальности и осложнений, которые они вызывают, а также присущих им трудностям, связанным с их диагностикой и лечением [1].

В настоящее время в развитых странах и Европе острые нейроинфекции у взрослых чаще всего вызываются вирусами – энтеровирусами, герпес вирусами, арбовирусами, вызывающими 70-90% всех случаев инфекционных поражений ЦНС [2, 3]. Наибольшее количество тяжелых случаев, с летальностью до 30% наблюдается при герпесвирусных нейроинфекциях [4].

Патогенез поражения тканей ЦНС во время острого нейроинфекционного процесса является мультифакторным, и зависит от этиологии заболевания, возраста больного, наличия хронических заболеваний и иммунодефицита [3-5]. Развитие нейроинфекции сопровождается опасными для жизни патофизиологическими реакциями, такими как отек головного мозга, нарушениями функции гематоэнцефалического барьера (ГЭБ) и развитием