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RESEARCH ARTICLE

DELAYED DIAGNOSIS OF IMPORTED PLASMODIUM VIVAX MALARIA MIMICKING REFRACTORY MIGRAINE

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Abstract

Malaria is referred to as imported malaria in countries outside malaria-endemic areas such as Morocco. The aim of our study was to highlight the importance of epidemiological data for the diagnosis of imported malaria. A 29-year-old moroccan female, presenting with a 3-month history of headache unresolved with usual analgesics, for which she was put on antidepressants and neuroleptics. She then presented to the emergency department with nausea, vomiting, abdominal pain, and fever. History and clinical examination revealed only mild abdominal pain with fever. Blood count showed anemia at 10.4 g/dl, MCHC at 34, MCH at 32, MCV at 90 fl and reticulocytes at 157920.Symptomatic treatment was given and the patient was referred to the haematology department for etiological diagnosis of her regenerative normocytic normochromic anaemia.Patient was then referred to Internal Medicine, the patient reported having visited Pakistan 1 year previously.In view of this situation, and taking into account the fact that she had travelled to a malaria-endemic area, a thin blood smear (TBS) and a thick blood smear stained with MGG were carried out urgently. A diagnosis of P. vivax malaria was established. Results were communicated immediately to the attending physician, and treatment was administered in an outpatient setting.

Introduction:-

Malaria is a febrile erythrocytopathy caused by a haematozoan parasite belonging to the genus Plasmodium and is spread to humans by infected female Anopheles mosquitoes [1].

There are five species of Plasmodium responsible for the disease in humans: P. Falciparum, P. Vivax, P. Ovale, P. Malariae and P. Knowlesi. Each of these species has a specific endemic area, some of which overlap [2].

Outside these areas, the term "imported malaria" is used. Imported malaria is a diagnostic and therapeutic emergency [3], given that a P. falciparum infection can lead to a severe and potentially fatal form of the disease [4].

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Falciparum is the most widespread form [5]. The second most common cause of malaria worldwide is Plasmodium vivax, and it is the leading cause of malaria outside Africa. [6] P. vivax infections can be severe and fatal. [7]

The World Health Organization (WHO) describes malaria as a preventable disease [8], which can be cured, but despite that, the estimated number of deaths attributable to malaria has reached 619,000 in 2021, with the African region being the most affected [9].

Symptoms can range from mild to life-threatening. Mild symptoms include fever, chills and headaches. [9] Severity criteria for malaria attacks are those defined by the WHO [10]: Impaired consciousness, peripheral signs of circulatory failure; abnormal bleeding; hemoglobinuria (dark red urine, hemoglobinuria on dipstick); renal failure (creatinemia > 265µmol/l and/or oliguria < 2.2 mmol/l); severe anemia (Hb < 5g/dl or Ht< 15 mmol/l ± pH < 7.35; hyperlactatemia: plasma lactates > 5 mmol/l; hyperparasitemia = 4% in non-immune patients; jaundice (clinical or total bilirubin > 50 µmol/l).

In Morocco, malaria is a notifiable disease [11]. Morocco was officially declared free of the disease in 2010 [12], and an average of 450 cases of imported malaria are registered annually [13].

Malaria is referred to as imported malaria in countries outside malaria-endemic areas such as Morocco. Expatriates and immigrants living in Morocco and returning from their country of origin are among the populations concerned, as are, in particular, occasional Moroccan travellers to sub-Saharan Africa and endemic areas. [10]

This case highlights the importance of epidemiological awareness and the need for a thorough medical history to diagnose malaria, including the possibility of a stay in an endemic zone.

Patient andMethods:-

A 29-year-old female Moroccan patient, married, primipara, under psychiatric care for 3 months for tension headaches, not controlled by the usual analgesics and treated with neuroleptics and antidepressants.

While still under treatment for her headaches, she presented to the emergency department with nausea, vomiting and abdominal pain, all of which were associated with fever.

Blood counts in the emergency department revealed normocytic normochromic anemia (Hemoglobin(Hg)=10.4g/dl, Mean Corpuscular Hemoglobin Concentration (MCHC) 34g/dl, Mean Corpuscular Hemoglobin Content (MCH) 32 pg, Mean Globular Volume (MGV) 90 fl and Reticulocyte Count 157.92G/L).

Symptomatic treatment with antipyretics and antispasmodics was administered, and patient was then referred to the Hematology Department for etiological diagnosis of her regenerative normocytic normochromic anemia.

Haemolytic anaemia was first suspected, and haemolysis work-up revealed a collapsed haptoglobin at 0.01 mg/dL, LDH at 450 IU/L and a negative Coombs' test; antinuclear and anti-DNA antibodies were negative. Our patient's etiological investigation was unsuccessful whil still ruling out a systemic disease.

The patient was then referred back to Internal Medicine for additional investigations. On further questioning, the patient stated that she had been in Pakistan 1 year ago, and reported a history of acute fever in Pakistan, for which she had received Primaquine on an outpatient basis. She acknowledged her non-adherence and reported that she stopped her treatment after 3 days. No documentation of this episode was provided.

Upon admission to the Department of Internal Medicine, patient was conscious, Glasgow score 15/15, pale complexion, conjunctival subicterus and fever of 39.5°C. Abdominal examination revealed generalized abdominal tenderness, neurological examination was unremarkable, and the rest of the clinical examination was uneventful. Abdominal ultrasound revealed splenomegaly. Complementary biological examinations yielded the following results: hemoglobin 8.2 g/dl, red blood cells 2.52 G/L, MGV 92 fl, MCHC 33.7g/dl MCH 33.7pg, leukocytes 4.13G/L, platelets 123G/L, reticulocytes 140 G/L. Hemolysis work-up revealed haptoglobin 0.001 g/L, LDH 500 IU/L, total bilirubin 28.48 mmol/L predominantly indirect bilirubin, SGOT and SGPT 3 times above normal, preserved renal function, inflammatory markers with C-reactive protein 24.5 mg/L.

Considering that the patient had been to a malaria-endemic area, the diagnosis of imported malaria was strongly considered, and a direct parasitological diagnosis was requested. The Giemsa-stained Thick Blood smear was positive, and the May Grunwald Giemsa-stained Thin Blood smear showed trophozoites, schizonts and gametocytes, and enabled identification of the Plasmodium vivax species. Calculated parasitaemia was low, below 1%. (Fig 1,2,3)

BIOSYNEX's Palutop +4 Optima® rapid immunochromatographic test for antigens (specify Ag) was also positive for P.vivax (Fig 4).

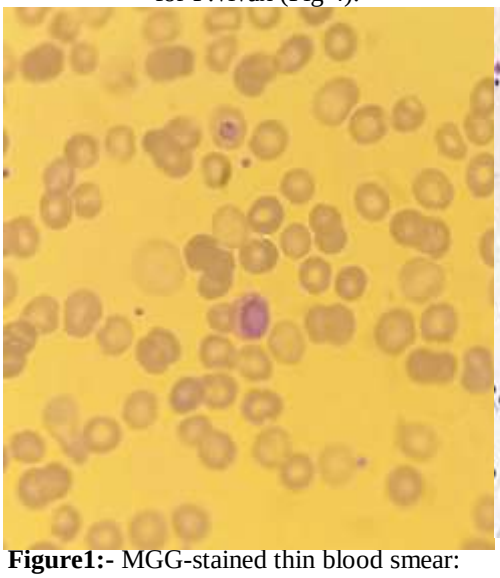

Figure1:- MGG-stained thin blood smear: P.vivax trophozoite and gametocyte.

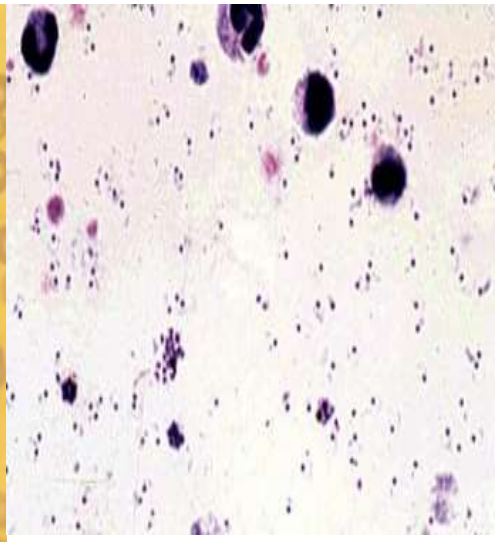

Figure 2:- Giemsa-stained positive thick smear showing Plasmodium haematozoa.

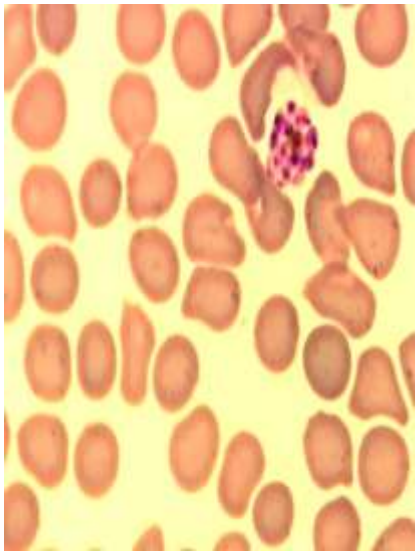

Figure 3:- MGG-stained thin blood smear: P.vivax schizont.

Figure 4:- Positive immunochromatographic rapid diagnostic test for P.vivax.

Plasmodium vivax malaria was confirmed and immediately notified to the attending physician. The patient was treated according to the Moroccan protocol: she was put on Primaquine 0.25 mg/kg from day 1 to day 14 to be taken

with meals, combined with Chloroquine for 3 days, at a dose of 600mg/d for the first two days and 300 mg on day 3 of treatment.

Evolution under anti-malarial treatment was satisfactory, reaching and maintaining apyrexia within 36 hours, with resolution of headache and abdominal pain. A follow-up blood work-up on day 21 revealed the following results: haptoglobin increased from 0.01 to 0.3 mg/L, LDH decreased to 200IU/L, and liver function status normalized. Hospitalization lasted 5 days, the patient finished her treatment on an outpatient setting and was seen again for follow-up after 2 weeks. Thick and thin blood smears were negative.Blood work was normal, with Hg 12.8, LDH 185 IU/L and CRP 7 mg/L.The patient reported no headache episodes since the initiation of treatment.

Discussion:-

Plasmodium vivax is prevalent in Latin America and Asia [14], and is the most challenging to eradicate due to its wide geographical distribution. P.vivax has reappeared in malaria-free temperate regions, including Greece, Corsica, the Korean peninsula, central China and Australia [15-16]. It is now estimated that 82% (11.7 million cases) of the global burden of P.vivax comes from four heavily affected countries: India, Pakistan, Ethiopia and Sudan. [14]

P. Falciparum is responsible for more than 90% of malaria in Africa. Duffy-negative blood type seems to protect against P. vivax species [13], the low prevalence of P. vivax in Africa could be explained by the high prevalence of the Duffy-negative blood type [14].

Plasmodium invasion relies on interactions between merozoite surface ligands and erythrocyte surface receptors[18]. Duffy antigen is an important molecule for erythrocyte invasion by P. vivax, and the absence of receptors on red blood cells reduces the risk of infection [17]. Binding of P. vivax Duffy-binding protein (PvDBP) to the erythrocyte Duffy antigen receptor for chemokines (DARC) leads to successful invasion [19]. P. vivax Duffy-binding protein (PvDBP) is an important functional factor in the invasion of parasites into Duffy/DARC-positive human red blood cells.

P. falciparum relies on a series of human red blood cell surface receptors for invasion, while P. vivax and P. knowlesi require interaction with the Fya or Fyb antigens of the Duffy blood group system. In Africa, where the Fy(a-b-) phenotype has achieved stability in different ethnic groups, transmission of P. vivax is rare [20].

However, a study involving P. vivax-infected individuals in a Duffy-negative population has suggested that P. vivax can invade erythrocytes using receptors other than the Duffy antigen [20]. The long-held assumption that the absence of Duffy antigen results in resistance to P.vivax malaria infection has been challenged by several studies. Gunalan, K. et al showed rare cases of P. vivax infection in Duffy-null African individuals. [22-23]

According to the study carried out in Morocco by Tlamçani I. et al, 66.7% of imported malaria cases are Plasmodium falciparum and in second place is Plasmodium ovale with a percentage of 23.3%. [24]

In our present case, we were dealing with imported P.vivax malaria in a young woman who had been in Pakistan more than a year earlier. Our patient presented with a mild malaria attack and showed unusual symptoms: at first, she complained of isolated tension headaches that were unresponsive to the standard analgesic treatments, and the onset of abdominal symptoms together with fever led us to investigate whether she had spent time in a malaria-endemic area, even if this was a long time ago. Failure to acknowledge her stay in Pakistan, as well as inadequate awareness of malaria epidemiology and of P. vivax recurrence, misled the doctor and delayed the diagnosis and proper therapeutic management of the patient.

Pakistan, the country of stay in our case, is endemic for malaria. Plasmodium vivax is the predominant species, responsible for 64% of malaria attacks, followed by P. falciparum with 34%. [25]

Malaria specialists have long acknowledged that incubation time depends on the plasmodial species involved, with a minimum of 7 days and generally less than 2 months for P. falciparum, and from 15 days to 10 months for P. vivax [26].

P.vivax shares the same parasitic cycles as the other species, with a distinctive feature in the intrahepatic phase when the parasite goes dormant for several weeks, months or years in hypnozoite form. Activation of the hypnozoites

leads to recurrences occurring weeks or even years after the primary infection. The mechanism of this reactivation is still unclear. [27]

Hypnozoites are the parasite's non-dividing hepatic form, which is responsible for recurrence and acts as a natural reservoir for human Plasmodium vivax and P. ovale malaria. During this dormant phase, patients are asymptomatic, parasites undetectable and insensitive to most antimalarial drugs. Once these parasites resume their development cycle, they are responsible for a new malaria attack, known as a reviviscence attack[28-29].

The diagnosis of malaria is usually made using a combination of epidemiological data (return from an endemic area), clinical signs, in which fever is a compatible but not exclusive argument, and parasitological evidence of the presence of Plasmodium. [30]

In many patients, prodromal symptoms of malaria infection may last 2 to 3 days, but may last longer in people with partial immunity or incomplete prophylaxis [31]. In our case, the patient had received anti-malarial treatment that had not been properly documented or taken, and she presented with tension headaches, for which she was sent for psychiatric care and treated with neuroleptics.

Typical malaria symptoms include fever, headache, nausea, vomiting, myalgias, anemia and jaundice. Clinical diagnosis of malaria can be complex due to the non-specificity of symptoms and their overlap with those of other febrile pathologies. [32]

Neurological disorders, respiratory distress or pulmonary oedema, circulatory failure or shock, haemorrhagic syndrome, hypoglycemia and renal failure are all signs of severity reported by the WHO [1]. The course of P. falciparum malaria can be fatal if treatment is not initiated early. Although P.vivax malaria is considered benign, it can lead to malaria with clinical symptoms similar to severe P.falciparum malaria. [33] In Western India, a retrospective study was carried out in an intensive care unit on 11 cases of severe P.vivax. Patients presented with cerebral malaria, renal failure, circulatory collapse, severe anemia, hemoglobinuria, abnormal bleeding and acute respiratory disorders [34].

Biological diagnosis of malaria remains an emergency, requiring identification of Plasmodium in a peripheral blood sample. Results must be available within a maximum of 2 hours, with close communication between the prescribing physician and the biologist[35].

Microscopic techniques combine thin smears, concentration techniques and parasite load calculations. Thin smears consist of a drop of blood spread on a slide, stained with May Grünwald Giemsa (MGG), Wright or Wright-Giemsa. Depending on staining, Shüffner granulations (P. vivax and P. ovale), Maurer spots (P. falciparum) or species-specific Ziemann dots (P. malariae) can be detected. This is the only technique that can simultaneously reveal the presence of the parasite, determine the parasite load and easily identify the Plasmodium species. Identification is based on the size of parasitized red blood cells and parasite stages. Typical detection threshold is around one hundred parasites per microliter. Readings should include at least 200 microscopic fields (immersion objective, x 100), given the frequency of low parasite loads. If thick blood smears are not available, the number of fields observed should be increased to 800 to achieve a similar sensitivity [36].

Thick smear is a manual technique in which parasites are condensed on a smaller surface area than the thin smear (concentration effect), and stained with Giemsa. This technique is more time-consuming and delicate to perform than thin smears, but increases the quantity of blood sampled, thus improving examination sensitivity when parasitaemia is low. Parasites' appearance makes it difficult to diagnose species using this method. One hundred microscopic fields (immersion objective, x 100) are sufficient, with a detection threshold of around ten parasites per microliter. Thin blood smears stained with May-Grünwald-Giemsa (MGG), combined with thick smears, are the gold standard for diagnosis. [37]

Parasite load must be determined for P. falciparum, as it helps to establish the severity of the infection. However, it is still recommended for other species to monitor therapeutic efficacy [36]. On blood smears, results represent the percentage of parasitized red blood cells out of the total number of red blood cells observed. It is more accurate on thick blood smears, where it is calculated using the leukocyte cell count as a reference. [35,36]

From the 1990s onwards, rapid diagnostic tests (RDTs) have become increasingly popular as diagnostic tools, particularly in resource-limited settings. [38]

RDTs are based on an immunochromatographic technique, which is inexpensive and takes an average of 10 to 20 minutes for interpretation from a drop of blood. Various formats are available: cassette, strip or reaction card. Typically, several different antigens can be detected on a single strip. RDTs detect proteins that can be synthesized either by a single species, or by several species.

Species-specific proteins: Histidine-rich proteins are produced by the blood stages of P. falciparum and contribute to the expression of "knobs" (erythrocyte membrane protuberances involved in the onset of severe malaria) [38]. The most commonly tested in RDTs is P. falciparum Histidin Rich protein-2 (PfHRP2) expressed by P. falciparum. [38].

Plasmodium aldolase, located in the membranes of schizontal stages, is common to all five Plasmodium species. It enables effective identification of P. falciparum and P. vivax, but is less sensitive to P. ovale and P. malariae. As a result, some manufacturers use an aldolase specific to P. vivax.

Plasmodium lactate dehydrogenase (pLDH) is a glycolytic enzyme synthesized in asexual stages and common to all five plasmodial species. Some tests target a specific molecular form of pLDH for P. falciparum and P. vivax [39].

RDTs come with both advantages and disadvantages, allowing the detection of one or more Plasmodium antigens in the blood. They also deliver rapid results, and do not require a qualified laboratory technician to interpret the results. RDTs are more sensitive to high parasite loads, and may be falsely negative in cases of low parasitaemia. [40]

High levels of rheumatoid factor or autoantibodies, as well as viral and bacterial infections, can lead to false positives. On the other hand, false negativities may occur if parasitaemia is low: the amount of circulating PfHRP2 may be below the RDT detection threshold. In the event of strong suspicion, microscopic concentration techniques should be used and testing repeated 24 hours later, allowing time for parasitaemia to rise to the RDT detection threshold. [39,41,42]

Several biological abnormalities are described during malaria attacks Hematological abnormalities are common, and blood counts are a fundamental test. [43]

Thrombocytopenia is a common finding in malaria. According to the study by Robinson et al, thrombocytopenia was present in 71% of malaria cases [44]. It can be used as a sensitive but non-specific marker for active Plasmodium infection [45]. P. Proença et al reported 70% of thrombocytopenia cases and 60% of hemolytic-type anemia cases in patients with malaria attacks. [46]

Anemia is a common disorder in patients with malaria. Its pathogenesis is complex and multifactorial [47,48]. Malaria is an intraerythrocytic parasite, thus parasite-containing red blood cells are subject to lysis upon schizont rupture. However, a more important factor is the accelerated hemolysis of non-parasitized red blood cells, that parallels the intensity of parasitization [49]. Cytokine production and remodeling of erythrocytes by Plasmodium ligands also play a role in the development of anemia [50].

One of the distinctive characteristics of P. vivax is its preference for infecting reticulocytes. CD98 has been identified as a reticulocyte membrane receptor for P. vivax reticulocyte-binding protein 2a (PvRBP2a) and has been strongly correlated with reticulocyte invasion by P.vivax[49]. Anemia due to chronic reticulocyte destruction is the main pathophysiological consequence of P. vivax malaria[51][52].

The increase in LDH during malaria is probably due to intravascular hemolysis[53]. Winters et al. found in their series an elevation of LDH in 83% of malaria attacks [54].

Hyperbilirubinemia, which is mainly secondary to intravascular hemolysis and rarely to liver damage, is quite common [55].

Treatment of non-complicated P. vivax malaria starts with chloroquine. Exceptions to this include infection contracted in chloroquine-resistant areas, principally Papua New Guinea and Indonesia [56]. Appropriate treatment

of non-complicated chloroquine-sensitive vivax malaria includes chloroquine phosphate or hydroxychloroquine combined with primaquine.

Due to the presence of P.vivax hypnozoites in the liver, primaquine must also be added to the treatment plan, and is contraindicated in G6PD-deficient patients and pregnant women. In cases of G6PD deficiency, primaquine can cause severe hemolytic anemia. Whether or not to use primaquine in this group of patients must be considered on a case-by-case basis. [57] In pregnant women, primaquine is contraindicated because of the risk of fetal hemolysis. [58] Treatment with primaquine should be delayed until after delivery. [59]

Conclusion:-

Good knowledge of geographical distribution and epidemiological patterns of the plasmodial species, and particularly the concept of late reviviscence seen with P.vivax and P.ovale, is essential for raising the diagnosis of imported malaria. It is therefore crucial that all healthcare professionals dealing with imported malaria are fully aware of the clinical and epidemiological aspects of this multi-faceted and potentially fatal parasitosis.

References:-

1. OMS. Paludisme (2018) (http://www.who.int/fr/newsroom/factsheets/detail/malaria)
2.Botterel F, Dardé M L, Debourgogne A. Delhaes L, Houzé S, Morio F et al (2017) Parasitologie et Mycologie Médicales - Guide des Analyses et des Pratiques Diagnostiques 2,2017,259-66
3. Laurent V, Hilly J, Bedel J, Planquette B, Legriel S et al (2014) Paludisme grave d'importation de l'adulte. Journal Européen des Urgences et de réanimation. 2014; 26(2): 97- 104. PubMed | Google Scholar
4. Société de pathologie infectieuse de langue française, Collège des universitaires de maladies infectieuses et tropicales, Société de réanimation de langue française. Recommendations for clinical practice. Management and prevention of imported Plasmodium falciparum malaria. Med Mal Infect 2008;38:39-117
5. Grands lignes du plan d'action de l'OMS pour la lutte contre le paludisme. 1993 - 2000. Conférence ministérielle sur le paludisme.Amsterdam. 27 octobre 1992
6. Maazoun F, et al. (2015)Splénomégalie palustre hyper-réactive. Rev Med Interne (2015)
7. A. Lover and Richard J. Coke (2013)Quantifying Effect of Geographic Location on Epidemiology of Plasmodium vivax Malaria Andrew Emerging Infectious Diseases Vol. 19, No. 7, July 2013 DOI: http://dx.doi.org/10.3201/eid1907.121674
8. Haute Autorité de Santé (2016). Évaluation des actes de diagnostic biologique des infections à Plasmodium décembre 2016. (https://www.hassante.fr/portail/upload/docs/application/pdf/2016-12/argumentaire_paludisme.pdf)
9 . Paludisme World Health Organization (2018). https://www.who.int/fr/news-room/fact-sheets/detail/malaria
10. Ministère de la Santé Publique du Maroc (2014) Guide de prise en charge thérapeutique du paludisme importé
11. World Health Organization (2010). Le Maroc certifié exempt de paludisme. REH 2010,85(24):235–6
12. La Direction de l'Epidémiologie et Lutte contre les Maladies, Bulletin d'épidémiologie et de santé publique (2017). Maroc,2017;40:74
13. Price Robert J. Commons Katherine E. Battle, Kamala Thriemer and Kamini Mendis (2020) Plasmodium vivax in the Era of the Shrinking P. falciparum N Trends in Parasitology, June 2020, Vol. 36, No. 6 https://doi.org/10.1016/j.pt.2020.03.009
14. Danis K, Baka A, Lenglet A, Van Bortel W, Terzaki I, Tseroni M et al (2011). Paludisme autochtone à Plasmodium vivax en Grèce, 2011. Euro Surveill. 2011; 16:19993 .PubMedLien externeGoogle ScholarLien externe
15. Hanna JN, Ritchie SA, Brookes DL, Montgomery BL, Eisen DP, Cooper RD(2004) Une épidémie de paludisme à Plasmodium vivax dans l'extrême nord du Queensland, 2002. Med J Aust. 2004; 180:24-8 .PubMedLien externeGoogle ScholarLien externe
16. Gunalan, K. et coll. (2018) Infections à Plasmodium vivax des érythrocytes Duffy négatifs : historiquement non détectées ou une adaptation récente ? Tendances Parasitol. 34, 420-429 6. Twohig
17. Gaur, D., Mayer, D. C., and Miller, L. H. (2004) Parasite ligand-host receptor interactions during invasion of erythrocytes by Plasmodium merozoites. Int J Parasitol 34, 1413-1429 12.
18. Miller, L. H., Mason, S. J., Clyde, D. F., and McGinniss, M. H. (1976) The resistance factor to Plasmodium vivax in blacks. The Duffy-blood-group genotype, FyFy. N Engl J Med 295, 302- 304
19. Carvalho GB, de Carvalho GB.(2011) Duffy Blood Group System and the malaria adaptation process in humans. Rev Bras Hematol Hemoter. 2011;33(1):55-64. doi: 10.5581/1516-8484.20110016. PMID: 23284245; PMCID: PMC3521437.

20. Zuo S, Lu J, Sun Y, Song J, Han S, Feng X, Han ET, Cheng Y et al (2024) The Plasmodium vivax MSP1P-19 is involved in binding of reticulocytes through interactions with the membrane proteins band3 and CD71, Journal of Biological Chemistry (2024) doi.org/10.1016/j.jbc.2024.107285.
21. Gunalan, K. et coll. (2018) Infections à Plasmodium vivax des érythrocytes Duffy négatifs : historiquement non détectées ou une adaptation récente ? Tendances Parasitol. 34, 420-429 6. Twohig,
22. Gunalan K, Lo E, Hostetler JB, Yewhalaw D, Mu J, Neafsey DE, Yan G, Miller LH (2016). Rôle de la protéine 1 de liaison à Duffy de Plasmodium vivax dans l'invasion des Africains Duffy-null. Proc Natl Acad Sci U S A. 2016 mai 31; 113(22):6271-6. [Article gratuit PMC] [PubMed]
23. Tlamçani I, Benjelloun S, Yahyaoui G, Benseddik N, Alami M, Moudden MK, Amrani Hassani M, El Baaj M, Er-ramiM (2014). High imported malaria incidence at a Moroccon military hospital Journal of Microbiology and Infectious Diseases 2014; 4 (2): 44-49
24. Ali Bin Sarwar Zubairi, Sobia Nizami, Afsheen Raza, Vikram Mehraj, Anita Fazal Rasheed, Najia Karim Ghanchi, Zahra Nur Khaled, and M. Asim (2013)Beg Severe Plasmodium vivax Malaria in Pakistan Emerging Infectious Diseases
25. Pike RM et al (1976) - Laboratory-associated infections : summary and analysis of 3921 cases. Health Lab Sci. 1976 ; 13 (2) : 105-14.
26. White NJ. Determinants of relapse periodicity in Plasmodium vivax malaria (2011). Malar J. 2011;10:297. http://dx.doi.org/10.1186/1475- 2875-10-297
27. Adeline C et al(2019) Hepatic spheroids used as an in vitro model to study malaria relapse Biomaterials(Elsevier)- Vol.216, pp 119221-119221
28. Baird JK. (2013)Evidence and implications of mortality associated with acute Plasmodium vivax malaria. Clin Microbiol Rev. 2013 Jan;26(1):36-57. [PMC free article] [PubMed] [Reference list]
29. Chagnon A et al (1999) Contribution de certaines anomalies biologiques au diagnostic du paludisme. Med Mal Infect. 1999; 29 Suppl 3: 302-6. PubMed | Google Scholar
30. Malvy D et al (2000)., Le Bras M. Plasmodies. Malaria. Formes cliniques, diagnostic. Encycl. Med. Chir., Maladies Infectieuses, 8-507-A-20, 2000, 16 p
31. Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM (2007). Vivax malaria: neglected and not benign. Am J Trop Med Hyg. 2007 Dec;77(6 Suppl):79-87. [PMC free article] [PubMed] [Reference list]
32. Zubairi AB, Nizami S, Raza A, Mehraj V, Rasheed AF, Ghanchi NK, Khaled ZNet al (2013). Severe Plasmodium vivax malaria in Pakistan. Emerg Infect Dis. 2013 Nov;19(11):1851-4. doi: 10.3201/eid1911.130495. PMID: 24188313; PMCID: PMC3837647.
33. Dhanpat K. Kochar, Vishal Saxena, Narvachan Singh, Sanjay K. Kochar, S. Vijay Kumaral (2005) Plasmodium vivax Malaria Emerging Infectious Diseases Vol. 11, No. 1, January 2005
34. Marie-Fleur Durieux (2018) Diagnostic biologique du paludisme, Actualités Pharmaceutiques,Volume 57, Issue 574,2018,Pages 25-29,
35. Groupe recommandations de la Société de pathologie infectieuse de langue française (SPILF)(2017). Prise en charge et prévention du paludisme d'importation. Mise à jour 2017 des RPC 2007. www.infectiologie.com/ UserFiles/File/spilf/recos/ 2017-palu-texte-fi nal.pdf
36. Assya Khermach,Hanane Khalki , Lhoussine Louzi , Ali Zinebi , Karim Moudden, Mohamed Elbaa (2017)Perturbations biologiques au cours du paludisme: à propos de trente cas The Pan African Medical Journal - ISSN 1937-8688. doi:10.11604/pamj.2017.26.174.9008
37. Boyce MR et al (2017) Use of malaria RDTs in various health contexts across sub-Saharan Africa: a systematic review. BMC Public Health. 2017 May 18;17(1):470. [PMC free article] [PubMed]
38. Houzé S et al (2015)Apport des tests de diagnostic rapide en parasitologie : intérêt et limite. Revue francophone des laboratoires. 2015;474:29-36.
39. Abba K, Kirkham AJ, Olliaro PL, Deeks JJ, Donegan S, Garner P, Takwoingi Y (2014). Rapid diagnostic tests for diagnosing uncomplicated non-falciparum or Plasmodium vivax malaria in endemic countries. Cochrane Database Syst Rev. 2014 Dec 18;2014(12).
40. Groupe recommandations de la Société de pathologie infectieuse de langue française (SPILF) (2017). Prise en charge et prévention du paludisme d'importation. Mise à jour 2017 des RPC 2007. www.infectiologie.com/ UserFiles/File/spilf/recos/ 2017-palu-texte-fi nal.pd
41. Haute Autorité de santé (HAS) (2016). Évaluation des actes de diagnostic biologique des infections à Plasmodium. Décembre 2016.
42. N. Bhandary Vikram GS, H Shetty (2011). Thrombocytopenia in Malaria: A clinical study Biomedical Research 2011; 22 (4): 489-491

43. Robinson P, Jenney AW, Tachado M, Yung A, Manitta J,Taylor K et al (2001). Imported malaria treated in Melbourn Austrlia: Epidemiology and clinical features in 246 patients. J Travel Med 2001; 8:76–81.73. Lewis SJ, Davidson
44. Al-Omar IA, Eligail AM, Al-Ashban RM, Shah AH (2010). Effect of falciparum malaria infection on blood cholesterol and platelets. Journal of Saudi Chemical Society. 2010; 14(1): 83- 89.
45. E PROEN A, T. CABRAL, G. DO CARMO, L. FERREIRA et R. XAVIER (1997)Le paludisme d'importation l'hopital de Santa Maria de Lisbonne (1989-1995) Med Mal Infect. 1997 ; 27, RICAI : 691-5
46. Thia Prameswarie, Muhaimin Ramdja, Dwi Handayani (2018) Hematologic profiles of Plasmodium vivax Malaria patients Gita Dwi Prasasty, Thia Prameswarie, Muhaimin Ramdja, Dwi Handayani12 Apr 2018-Vol. 2, Iss: 2, pp 8-15
47. Blanc NJ (2018). Anémie et paludisme. Malar J. 19 octobre 2018 ; 17(1):371. DOI : 10.1186/S12936-018-2509-9. PMID : 30340592 ; PMCID : PMC6194647.
48. Kasturi Haldar Narla Mohnadan et al (2009) Erythrocytic infection and anemia 01 Jan 2009-Hematology (American Society of Hematology)-Vol. 2009, Iss: 1, pp 87-93
49. Jakub Gruszczyk et al(2018).Le récepteur 1 de la transferrine est un récepteur spécifique des réticulocytes de Plasmodium vivax.Science359,48-55(2018).DOI: 10.1126/science.aan1078
50. Martha A Clark , Usheer Kanjee , Gabriel W Rangel and al (2021) Plasmodium vivax infection compromises reticulocyte stabilityDOI: 10.1038/s41467-021-21886-xNATURE COMMUNICATIONS | (2021) 12:1629
51. Hemmer CJ, Holst FG, Kern P, Chiwakata CB, Dietrich M, Reisinger EC (2006). Stronger host response per parasitized erythrocyte in Plasmodium vivax or ovale than in Plasmodium falciparum malaria. Trop Med Int Health. 2006 Jun;11(6):817-23.
52. Chagnon A et al (1999) Contribution de certaines anomalies biologiques au diagnostic du paludisme. Med Mal Infect. 1999; 29 Suppl 3: 302-6. PubMed | Google Scholar
53. Winters RA, Murray HW et al (1992). Malaria- the mime revisited: fifteen more years of experience at a New York City teaching hospital. Am J Med. 1992; 93(3): 243-6. PubMed | Google Scholar
54. Olivier Bouchaud (2018). Fièvre au décours d'un voyage en zone tropicale Revue francophone des laboratoires N° 500 MARS 2018 https://doi.org/10.1016/S1773-035X(18)30092-3
55. Chu CS, White NJ (2021). The prevention and treatment of Plasmodium vivax malaria. PLoS Med. 2021 Apr 23;18(4):e1003561. doi: 10.1371/journal.pmed.1003561. PMID: 33891587; PMCID: PMC8064578
56. Recht J, Ashley EA, White NJ(2018). Use of primaquine and glucose-6-phosphate dehydrogenase deficiency testing: Divergent policies and practices in malaria endemic countries. PLoS Negl Trop Dis. 2018 Apr;12(4):e0006230.
57. Baird JK, Hoffman SL (2004). Primaquine therapy for malaria. Clin Infect Dis. 2004 Nov 01;39(9):1336-45.
58. Kovacs SD, Rijken MJ, Stergachis A. (2015) Treating severe malaria in pregnancy: a review of the evidence. Drug Saf. 2015 Feb;38(2):165-81.