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Malarial Related Myopathies: A Rhabdomyolysis Story

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Author's contribution

This work was carried out in collaboration among by the author. Author FES designed the review, performed the literature searching, screening all the potential literature, did the advances search and reading of all related and collected potential articles, checking the statistical analysis, wrote the initial draft, re-write and changed part of the draft until it reach the final manuscript. Author read and approved the final manuscript.

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ABSTRACT

Malaria is amongst the most prevalent and epidemiologically relevant global parasitic protozoan infections. It is infecting millions of people annually, especially in south east Asia and sub Saharan Africa. Its morbidity and mortality still cannot be controlled entirely and elimination is still far away. Children and pregnant women are among the most vulnerable group in the population. Its pathobiology have related to cause direct or indirect deleterious effect on the patient's skeletal muscle, named rhabdomyolysis. Eventhough it is very rare, but potentially fatal and lethal. Three mechanism of malaria related rhabdomyolysis are very intense inflammatory response, extensive red cells sequestration in muscle capillaries due to severe anemia and the parasite toxin's, will lead to or add risks of complication. Derangement of specific type of muscle, named the skeletal and cardiac, is amongst the earliest sign of severe malaria. Further study need to be conducted in the future, especially on important topics about mechanism and its effect, signaling pathways, best practice on laboratory approach and management strategy best practice.

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1. INTRODUCTION

In human, there are already known 5 species of Plasmodium that can caused infection, namely *Plasmodium falciparum, P. vivax, P. ovale, P. malariae,* and *P.knowlesi* [1,2]. The disease is still most prevalent in many region globally, especially in Southeast Asia and Sub Saharan Africa [3]. Its global morbidity and even mortality remains high, especially in the endemic region where constant transmission occurred [4]. Pregnant women and children are the most vulnerable group, but also travellers traveling to endemic tourist area, the latter categorized as imported malaria [5,6]. There are achievement on effort being made to eliminate malaria, but dynamic and variation on climate or certain region specific factors may jeopardise the ability to abide righteous track to achieve global elimination of malaria parasite [7].

By the help of a vector species, this disease occurred through the bite of *Anopheles* spp mosquito that transmitted this blood borne protozoan to humans. In brief, malaria causes several subjective complaints from the patients, including fever, chills, anemia related complaints, e.g malaise, headaches, weakness, fatigue and the last one that cannot be underestimated named myalgia [8].

Myalgia is a subjective and at the same time also objective muscular complaint, and it is not always prominent [1]. In severe form of malaria, although very rare, a condition of myalgia related rhabdomyolysis with myoglobinuria and skeletal muscle necrosis can occur; sometime it precede renal failure secondary to acute tubular necrosis, a very fatal complication of untreated malaria, found on both vivax or falciparum malaria [9-11]. It must be kept in mind once again, it is not species specific [9-11]. It can happened whenever the patient's condition get worse, even when the patient already in the intensive care unit [12,13]. This disease is quite unique and the deterioration of the history of the disease course can happened so fast, it is very important for clinicians to be aware on this condition, because if untreated it can caused mortality to the patient [14].

The aim of this review is to refresh the knowledge on pathogenesis of malaria related rhabdomyolysis and to reveal three mechanism known to be responsible to caused malaria related rhabdomyolysis: (1) very intense inflammatory response, (2) infected red blood cells sequestration in muscle capillaries due to severe malaria related anemia and (3) the parasite toxin's, that will lead to or complicating more on this already potentially fatal effects. Further discussion also on other tests that might contribute to making correct diagnosis of rhabdomyolysis.

2. PATHOGENESIS OF MALARIA RELATED RHABDOMYOLISIS

Malaria pathogenesis is a process by which the first time mosquito injected malaria parasites, enter the host's body and cause illness. It evades the host's immune system by its obligate intracellular properties by causing infected red blood cell (IRBC) started to losing its deformability properties, then it makes IRBC easy to attach to the microvasculature wall and then followed by rupture/lysis of the IRBC, a condition known as sequestration [8].

Common malaria without complication consists three classic symptoms namely intermittent high fever, anemia and splenomegaly. Commonly, sweating and chills when temperature rises came, and so often other symptoms found, e.g headache, malaise, nausea with or without vomiting, fatigue, and muscular pain or weakness. In certain condition, severe malaria with complications can happened, especially in vulnerable group of the population, *e.g* children and pregnant women. the spectrum of the disease can develop to condition as follows: severe anemia, seizures, respiratory distress, cardiovascular collapse, shock and multi organ failure (kidney, liver, heart failure) with cerebral malaria/coma [13,15]. Based on its size, the human musculature is the biggest size among all organ-system of the human body and, as expected, in severe and complicated untreated malaria can significantly affects metabolism function, including the skeletal muscle functions [16]. Actually, many separate symptoms of malaria can contribute to the skeletal and cardiac system malfunctions, independently, and or simultaneously. This condition showed us the impairement of immunological balance of the host due to malaria parasite [17].

Rhabdomyolysis actually is a syndrome that can occur rapidly and may develop from a variety of causes [18,19]. Rhabdomyolysis is a well-known

clinical syndrome of muscle injury associated with myoglobinuria, electrolyte abnormalities, and often acute kidney injury (AKI). The pathophysiology involves injury to the myocyte membrane sheath and/or changed energy production that results in shifted and increased intracellular calcium concentrations and initiation of destructive processes of the skeletal cell mass that further reduced its size.

The classic findings consist of unspecific muscular complaint (aching/pain), fatigue, weakness and urine discoloration (resembles tea-coloured). It is not specific and may not always be found [18]. The making of correct diagnosis, as other illness, therefore rely on information gathered from the anamnesis (history of specific muscular pain), physical examination (weakness) and from the laboratory or other supportive examination. All information supposedly lead to the presence of unusual muscular complaint, any suspicious physical tests with odd laboratory values of muscle related enzyme [18,19]. An increased in plasma *creatine kinase* (CK) level perhaps being a warning for a serious muscular injury condition [20]. On the other hand, the condition of Hyperkalaemia, the sign of acute renal failure and any condition related to compartment syndrome or muscle lysis and break down when present, may represent the major life-threatening complications, eventhough still not specific [21].

In order to prevent the clinical deterioration of susceptible patient, the clinical management rely on maintaining normal vital sign, rapidly given antimalarial therapy after a definite diagnosis being made, manage aggressive fluid resuscitation, and prevent any complication to develop, all of these establish as soon as possible [22]. Although the causes of rhabdomyolysis are so diverse, where malaria can be one of them, the initial pathogenesis emerge to follow an obviously final common pathway, ultimately directing to pronounce and extensive muscle cell destruction and drag the broken muscular components enters the closed circulation system, so it can be measured in the serum [23].

In the normal musculature system, structurally, a sub microscopic sheer membrane exists and surrounded all striated muscle fibres (named the sarcolemma). This sheer of membrane physiologically contains numerous built –in pumps that control and made constant cellular electrochemical ionic charge; that resulted in electric gradients of the cell that maintained constant all the time, homeostatically. For example, the concentration of the ion Na inside a cell normally always preserved at the concentration as many as 10 mEq/l by the active action of a pump of sodium-potassium adenosine triphosphatase (Na/K-ATPase) which located in the region of sarcolemma. Na+/K+-pump is an electrogenic transmembrane ATPase that actually located in the outer plasma membrane of cells [24]. This readily active pump of Na/K-ATPase move Na from the inside part the cell to the exterior region of the cell. That act made the inner part of the cell is always being more negative than in the outer part of the cell; this is due to the positive charges that are being actively transported and being pumped out across the membrane [24,25]. The gradient draws the ion Na inside and switch with the ion Ca. This exchange conducted thru a channel of ion exchange, separatedly [25]. Furthermore, the condition of low intracellular Ca levels are also keep by Ca2+ ATPase pump, an active Ca exchanger pump that helps Ca entry into the organelle named mitochondria and endoplasmic/ sarcoplasmic reticulum [26,27]. The flow of intracellular calcium (Ca^{2+}) is critical for the activation and regulation of crucial biological activities that are mandatory in any living organisms. As the major Ca^{2+} repositories inside the cell, the endoplasmic reticulum (ER) and the sarcoplasmic reticulum (SR) of muscle cells are central in maintaining and amplifying the intracellular Ca^{2+} signal [27].

The complex processes which has previously been discussed rely on the availability of energy carrying molecules, the ATP, as the primary source of energy [28]. The systemic end result of most conditions in terminal rhabdomyolysis, named ATP depletion/run out, which appears to be resulted in Na/K-ATPase and Ca2+ ATPase pump error [29,30]. Finally, the equilibrium state is marked by an higher tolerance to Na ions by the cell due to either derangement/ discontinuation of the plasma membrane or diminished cell's production of ATP/burn out [31,32].

Aggregation of the ion Na inside the organelle cytoplasm then shifted the equilibrium into an increase of Ca, intracellularly [27-29]. This excessive calcium in the part of the cell then immediately triggers intracellular proteolytic enzymes to be ready and active, that in turn "auto-digest" the host's muscle cell, directly [33]. This action caused the muscle cells to

degenerate rapidly, and as the myocyte lysis and took place, and together with large amount of potassium, aldolase, phosphate, myoglobin, CK, lactate dehydrogenase, aspartate transaminase and urate are leak into interstitial fluid, across the membrane and then immediately enter into the circulation [34]. Experts believe, this condition caused the muscular complaint of the patient (e.g weakness and muscular pain) [34,35].

During physiological resting state, the plasma concentration of myoglobin is actually very low. If certain amount of skeletal muscle is damaged at once, then the circulating myoglobin levels immediately surpass the abilitiy of protein-binding capacity of the plasma, means that the plasma cannot able to bind it (so the myoglobin is in free-state condition, unbound) and then when it reach the kidney, it can start the process of precipitating in the glomerular filtrate [29]. This is a very dangerous condition for the homeostasis of the kidney [29,30]. Immediate excessive concentration of myoglobin in the specific region of the kidney may thus cause direct series of derangement consist of (1) massive obstruction in numerous tubular of the kidney, (2) direct nephrotoxicity, and the last but not least (3) acute renal failure [29,36].

The etiological spectrum of rhabdomyolysis is extensive; in many cases, simultaneous and extensive multiple muscle disturbances are usually needed to produce rhabdomyolysis unless an underlying myopathy is present [19,29,30]. This condition can be caused by severe form of malaria, a condition of complicated malaria (perhaps due to the unnecessary delay in making the correct diagnosis or lack of therapy) which took place suddenly if no immediate and sufficient patient management given to the vulnerable patient of malaria.[37] To some complicated malaria patient, this condition took place so fast and almost masking by other complaints, e.g loss of consciousness and or acute renal failure [14,15,37].

Three mechanism known to be responsible in which this blood protozoan able to caused rhabdomyolysis: (1) very intense inflammatory response, e.g associated pro-inflammatory cytokine production and oxidative stress, alone or in combination (2) infected red blood cells sequestration in muscle capillaries due to severe malaria related anemia and (3) the parasite toxin's, will lead to or complicating more these potentially fatal effects.

2.1 Very Intense Pro-Inflammatory Response to Malaria in Muscular Section

The pathology seen in all of these infectious diseases being explained by activation of the inflammatory system, with the balance between the pro and anti-inflammatory cytokines being tipped towards the onset of systemic inflammation [16,17]. Although not often expressed in energy terms, there is, when reduced to biochemical properties, wide agreement that infection with any kind of malaria species, is so often can be lead to fatal condition because the patient's severe condition failed the mitochondria to generate sufficient ATP to maintain normal homeostasis cellular function, starting from the cellular organelle level [38].

Common expertise opinion about above mentioned statement is because so many infected erythrocytes that become extensively sequestered at almost in the same time after being parasitized for a certain time and failed to survive, this condition prevent sufficient oxygen supply to reach area/regions it is needed the most [39]. So it is the condition of demand out numbered supply [40]. The evidence that an equally or more importantly why ATP deficiency arises rapidly in malaria cases that immediately developed into severe form, a condition supposed to be preventable. The clinical authority were expected to make a fast and correct diagnosis and collaborating in a team of experts working together handling the patient dynamics; to prevent the patient suffered furthermore because the patient were very prone to fall into complications (*e.g* severe anemia).

It is an inability of mitochondria, through the effects of inflammatory cytokines on their function, to utilise available oxygen, that precede the myopathy among severe malaria patients [41]. The activity of these cytokines, plus their capacity to control the pathways through which oxygen supply to mitochondria that are also restricted [42]. In malaria particularly through directing infected erythrocyte sequestration and driving severe anaemia, all together combine to make severe malaria primarily an inflammatory cytokine-driven disease and caused a cytokine storm that without proper and immediate management will caused a dangerous and lethal condition for the patient [43].

Systemic inflammation and sequestration of parasitized IRBC's are central in the

pathophysiology of severe *P. falciparum* childhood malaria, eventhough it is still not understood why some children are more at risks to develop malaria complications than others [44]. To identify human proteins in plasma related to childhood malaria syndromes, analysis of multiple specific proteins in plasma from hundreds of infected children were conducted. The existence of increased levels of specific muscle proteins in plasma strongly suggested potential extensive muscle breakdown and microvasculature lesions during the course of cerebral malaria [19,21,33,34]. Markers of oxidative stress were also found increased extremely related to severe malaria anemia while markers of endothelial activation, platelet adhesion and muscular damage were identified in relation to specific population of the patient namely children which suffer from cerebral malaria [44]. These findings suggest the presence of generalized and immediate vascular inflammation, vascular wall modulations with all of its consequences, activation of vasculature endothelium and unbalanced glucose metabolism that took place simultaneously and immediately in severe malaria [45-47]. Without proper management, such patient can easily drop and failed to be saved.

2.2 Infected Red Blood Cells Sequestration in Muscle Capillaries Due to Severe Malaria Related Anemia

The sequestration of Plasmodium– IRBC's in the microvasculature of vital organs is associated with severe conditions of disease; correspondingly, the molecular basis of IRBC's adherence to host tissue, and then break down, condition also known as sequestration, occurs in small capillaries and post-capillary venules of specific vital organs such as the kidney, brain and lungs [48,49]. This condition took place whenever the IRBC's losses its deformability properties due to the obligate intracellular parasite that inhabit and parasitize inner proportion of the cells; this condition preceed cytoadherence of IRBC'S to vascular cell wall [50]. Sequestration has been correlated with two condition, namely (1) mechanical obstruction of blood flow in small blood vessels due to certain condition (in this context, Malaria) and (2) rapid and systemic vascular endothelial cell activation, which may lead to its pathology [51].

As sequestration appears to be a signature of severe disease, the factors that mediate IRBC's adherence to endothelial cells in general can be divided into (1) parasite proteins (ligands) and (2) host endothelium proteins (receptors, adhesins) that are directly involved in the sequences of sequestration. Other important features that might contribute to and play an important roles in intravascular erythrocytes sequestration, e.g affinity/avidity of binding, tissue distribution of such this potentially fatal condition, polymorphisms of receptors and ligands and also their interactions, etc [48]. Microvasculature obstruction and endothelial activation are two important key point that will precede fatality to the patient [51,52].

As suggested by Hanson et al. [52] that microvascular obstruction and systemic endothelial activation are independently associated with plasma lactate, the strongest predictor of death in adults with severe falciparum malaria. This supports the hypothesis that the two processes separately make an independent but important contribution to the pathogenesis and the deterioration of the clinical manifestations of the disease [46,49,52].

In the future, the understanding of all of these condition and its sequences step by step, will help scientists in the development of new approaches that can either lead to complete full protection or at least reduce the global prevalence of Malaria, e.g through the development of vaccines or small molecule inhibitors that able to prevent red cell sequestration due to obligate intracellular malaria, that play a vital role in worsening of the disease.

2.3 The Parasite Toxin's: *Glycosylphosphatidylinositols*

According to Schofield and Hackett [53] were among the first to recognize the toxin of *P. falciparum*; a substance consists of glycolipid dominant toxin. They named it *glycosylphosphatidylinositol* (GPI), as the biochemical properties of the toxin. Any portion of parasite GPI's, free or linked with with any protein, will trigger a cascade of (1) activation of pro-inflammatory cytokines, *e.g* tumor necrosis factor and IL-1, and (2) activation of the macrophages and (3) up-regulates glucose metabolism in fatty tissue [53-55]. Cytokine induction can be diminished/prevented by deacylation with specific phospholipases, as do protein kinase C inhibitors [53]. *In vivo*, the parasite GPI's induces the cytokine release that further causing transient hyper-pyrexia and as

the final consequences is the condition of hypoglycemia [56]. When administered together with sensitizing agents in certain dose, together it can elicit a profound and potentially lethal cachexia for the host. In hospital basis, this is the condition that might happened when susceptible patient suddenly deteriorate clinically due to a series of condition caused by this GPI.

Furthermore, the GPI, phosphoglyceride toxin of Plasmodium's parasite, in fact is a very strong and potent glycolipid toxic substance for the host that may be responsible for a novel and yet, unrevealed mechanism of pathogenicity. The utilization of its pleiotropic effects on a variety of host's cells, *e.g* by ability to change the endogenous GPI-based second messenger/signal transduction pathways [53]. Any antibody that able to inhibit/prevent this GPI toxic properties, suggesting the prospect of a the making/ development of an antibody based antiglycolipid vaccine, that might work against malaria [57].

Glycosylphosphatidylinositol toxin of *Plasmodium* spp. directly increased several molecules, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin expression, all interfere with vascular endothelial cells and increased the level of leukocyte and induced cytoadherence via the enzyme tyrosine kinase-dependent signal transduction [51,55]. Thus further more, it also activates vascular endothelial cells through other pathway, named the tyrosine kinase-mediated signal transduction. By doing so, this leading to the activation of NF kappa B/c-rel and suppress the expression of adhesins. All of this conditions also related to the formation of cerebral malaria [54].

Other effect of malaria toxin causes hypoglycemia and induction of tumor necrosis factor [42,47]. Extracts of IRBC'S which were further co-eluted and co-purified with one of the two subtypes of mammalian insulin-mimetic *inositolphosphoglycans* similarly induced fibroblast proliferation in the absence of serum. In addition, induction of tumor necrosis factor in macrophages by malaria toxin and by lipopolysaccharide from the bacteria *Escherichia coli* was enhanced by pre-treatment of these toxins with α-galactosidase [58]. Thus, IRBC's contain both soluble *inositolphosphoglycan*-like insulin second messengers and endotoxin-like lipidic molecules [59]. This statement revealed to us that even the toxin located deep inside the host cells, it still have the ability to induced immune reaction and caused a deterioration effect to the host directly [48].

The better understanding of malaria toxin, *Glycosylphosphatidylinositols*, in malaria pathogenesis and immunity, will help in the development of successful potential agent for therapeutic inhibition and even perhaps vaccination.

3. THE DISRUPTION OF SPECIFIC TYPE OF MUSCLE: SKELETAL AND CARDIAC

Malaria in humans whenever become worse can develop to a series of serious conditions: weakness, fatigue, pronounced muscle cell lysis that can lead to skeletal-cardiac myopathies, acute respiratory distress, kidney-liver-multi organ failure, and coma even death [8-11]. Skeletal muscle damage classified as severe complications of Malaria, besides the more readily recognized effects on sequestration of erythrocytes causing severe anemia [15,16].

The reasons why muscular system is prone to malaria is due to its size compared to other organs in human body, its rich blood supply which supported by many blood vessels and the last but not least that its complex activity related to other important function of the human body, e.g respiratory, circulatory and digestion [19]. All of these showed us how complex the daily routine activity of normal muscle. We can imagine if to that previously normal muscle then adding local profound ischaemic, inflammation and oxidative stress due to extensive sequestration of malaria IRBC's intravascularly that took place in the same time; and it will also increased the levels of serum creatine kinase and further but quickly destroyed the prone muscle; starting in the cellular or even molecular level which caused the reduction of muscle content/muscle mass [21-23]. Further analysis also showed that there is an essential contractile proteins found in the serum; the potential biomarkers of the broken and damaged skeletal and cardiac muscles [33,34]. In the future, with better understanding about the functions and effect of musculature related biomarkers, it might be useful as (1) indicator of preventive tools to avoid complications and maybe to (2) determine the effectiveness of management interventions of the patients (pharmacologically and non-pharmacologically) and even perhaps (3) to secure the organ of heart and musculature from malaria-induced damage [35].

According to Marrelli and Brotto [60], the injured skeletal muscles has specific biomarkers relating with the severity rate of malaria infection (among all fifth, *P. falciparum* is the most prominent in causing this severe condition), and central to this condition is the sequestration of IRBC's [48,50,51], Pronounced elevation in blood creatine kinase (CK) directly affect the muscles [33-35]. CK is an enzyme that facilitate in the production and usage of ATP, the miracle molecule of energy-provider to the living cells; and without question, it is predominantly found inside the cells of cardiac and skeletal muscles [61]. One longitudinal study suggested that falciparum malaria is associated with skeletal muscle damage in the susceptible host. The increased level of CK happened during the course of the disease and it directly associates with abnormalities of the muscle [62]. In addition, the pro-inflammatory characteristic of malaria, marked by increased pro inflammatory cytokines levels (such as tumour necrosis factor, TNF) in combination with the formation of highly damaging free radicals should be considered as potential important mechanism of damaged muscle cells with its related complaint, *e.g* weakness, fatigue, loss of mass [41,43,48, 56,58,61].

In the context of skeletal muscle, biochemical checking of paramater on skeletal muscle damage is usually found in malaria, but the condition of pure rhabdomyolysis appears to be very scarce; means that it can be prevented as long as the management is correct and given as soon as possible.

There is relationship between serum *creatine kinase* and myoglobin concentration, muscle histology appearance, and renal function in three types of clinical malaria: cerebral, severe (non cerebral) and non severe form of *P. falciparum* infections. By performing a muscle biopsy specimen for thorough examination under light microscopy and or electron microscopy, the histological appearance can be closely examined. The laboratory result showed us that the mean serum creatine kinase concentrations were raised but the condition similar in the severe or non severe patient, mean this parameter is not specific. The mean serum myoglobin level was highest in patients with cerebral malaria, compared to other condition of malaria (uncomplicated or complicated). There was a strong correlation of myoglobinemia level with the mean serum creatinine level. The number of intravascular parasites, proportion of the mature forms, and glycogen reduction were highest in biopsy specimens that came from patients with cerebral malaria. Myonecrosis was not found to happen in all three group of patients [63]. To this group of researcher opinion, muscle appears to be an important site for *P. falciparum* sequestration, but to my own personal opinion, actually it is the extensive erythrocyte sequestration in the numerous microvasculature of the muscles, and not only the muscle as single entities, which could contribute to further fatal metabolic and renal complications.

Prospective study conducted by Ray et al. [64] showed us that by assessing the cardiovascular system of the malaria positive patients, these researcher can followed up what is the effect of malaria (vivax or falciparum) on cardiac function. The examination conducted by sequential clinical examination, chest X-ray, ECG and transthoracic echocardiography. Total 272 cases of positive malaria that followed prospectively. As much as 26% patients were found to be suffering from circulatory failure, out of which one was *P. vivax* case and rest were cases of *P. falciparum* infection with high parasite density. One patient died due to cardiovascular collapse. ECG revealed sinus bradycardia in 7% of the cases, on the contrary, extreme tachycardia in 3.7% of cases and premature arterial ectopic with tachycardia in 3.7% of patients (p <0.05). The echocardiographic findings were global hypokinesia with decreased left ventricular ejection fraction in 11.1%, grade 1 left ventricular diastolic dysfunction in 3.7%, mild tricuspid regurgitation (TR) with mild pulmonary artery hypertension (PAH) in 3.7% and mild pericardial effusion in 3.7% of the cases. The ECG and echocardiography changes indicated myocardial involvement in severe malaria. The most common finding in ECG was sinus tachycardia which was present in about 40% of the patients at the time of admission which settled down to the normal range within two to three days of treatment. While the significant echocardiographic findings were global hypokinesia with decreased left ventricular ejection fraction (< 55%) in 3 (11.1%) cases. From this point of view, we can see that their incredible findings gave us a very rich information in the context of conducting research with limited number of patient; it will be very interesting if we can withdraw the result in to a more wide and complex population.

4. OTHER EXAMINATION THAT MIGHT HELPED IN MAKING CORRECT DIAGNOSIS OF RHABDOMYOLISIS

In terms of malarial related diagnostics, specific urinalysis test seems to be forgotten. Actually among clinicians, urinalysis is a poorly reviewed diagnostic tool in malaria patients; even though its application can actually revealed the presence of co-morbid conditions found in severe malaria, as the approach conducted by a Colombian group of scientist [65]. By analyzing the results of urinalysis examination that was performed in a total of 620 positive patients diagnosed with malaria by using thick blood smear analysis; complications were classified according to WHO major criteria for severity and minor criteria according to the Colombian malaria guideline. They found out that as listed in Table 1.

There was also found the condition of severe or moderate liver and renal complications that were associated directly with proteinuria and bilirubinuria. Urobilinuria was also associated with thrombocytopenia and neurological and hepatic dysfunction of the patient, eventhough that it must be examined closely whether the condition of this neurological and or hepatic derangement is caused by malaria or other illness. Ketonuria was associated with neurological dysfunctions. Their conclusion was the most frequent alterations found in the urinalysis of malaria infected patients were bilirubinuria, proteinuria, urobilinuria, and increased specific gravity, related to thrombocytopenia and liver, kidney, and neurological function alterations [65]. This information encouraged us that a more holistic analysis can be done by adding an additional examination that might be supportive for making the final and correct diagnosis.

Eventhough that all of these parameter were not specific, but it can help clinicians with additional information that might supported other results of examination. Maybe for regular self-financing patient, paying extra for further laboratory or radiology examination which seems incompatible with the course of the disease will cause the patient's or the family's objection. But in the universal health coverage system, this option might have a better chance to be conducted, depends on the doctor's ability to find the matched required laboratory or Radiology or other further examination in the coding system.

5. FURTHER INSIGHT IN THE FUTURE OF MALARIA RELATED RHABDOMYOLYSIS STUDY

This mini-review article already revealed some conditions found related to skeletal and cardiac muscle derangement in severe form of malaria. We've all heard the phrase "something old, something new, something borrowed and something blue". It's the list of items that no bride wants to walk down the aisle without; and in the context of malaria related rhabdomyolysis study, all of the condition already discussed must be kept in mind as important because no doctor wants to give their service to malaria patient without proper knowledge on malaria pathogenesis and its complication, including rhabdomyolysis.

Combination of local but extensive ischaemia, inflammation and oxidative stress damage with the central underlying condition is sequestration

Table 1. Lists of clinical condition of malaria as the result of urinalysis examination [65], modified

Clinical condition as the result of urinalysis examination	Percentage (%)
Severe or moderate clinical complications	31.3%
hepatic dysfunctions	25.8%
anemia	9.8%
thrombocytopenia	7.7%
renal dysfunction	4.8%
neurological and pulmonary complications	2.1%, 2.4%
hypoglycemia	1.1%
acidosis	40%
Bilirubinuria (+urobilinuria, proteinuria, and increased specific gravity)	24.3%
urobilinuria with ↑ serum bilirubin & alanine aminaminotransferase	30.6%
Proteinuria, associated with ↑ blood urea nitrogen, serum bilirubin,- -aspartate, alanine-transaminase, hematuria, and increased specific gravity	39.2%

of infected red blood cells due to intracellular protozoan plasmodium spp in microvasculature of human skeletal and cardiac muscles, that happened extensively in the context of skeletal muscle, leading to the pronounced degradation of vital proteins of the muscle and afterward being released in to the circulatory system, and this in turn is responsible for the sequence of extensive muscle breakdown and losing its function.

Further study must directed on (1) the finding of molecular mechanism of direct and indirect harm to the properties of contractile machinery and its function (2) if there is any, the genetic signaling pathways/networks regulating these sequences of conditions, (3) valid and reliable specific laboratory or other tests to make fast and correct diagnosis and the last but not least (4) novel management strategy to neutralized or even prevented this deterioration, maybe with molecular therapy or specific vaccine, or new drugs carefully designed to prevent the muscle damage, dietary interventions and or specific exercise training modalities to improve the patient's condition. These simple questions and many more question to come and how malaria still become a global health problem clearly shows the need for widely open further studies in many areas related to malaria; and one of them will be to determine the specific cellular and molecular mechanisms of malaria induced muscle damage.

5. CONCLUSION

Malaria is still a global health problem. Its morbidity and mortality remain high, especially in endemic region. From several form of complication in severe malaria, rhabdomyolysis rarely found but actually it is a potentially fatal condition without proper and immediate treatment. The patient complaint sometimes unspecific and probably masking by other more serious and clear clinical sign and symptom, so the doctor probably pay more attention to a more prominent clinical condition. In the future, further study need to be conducted, especially in the molecular mechanism that is responsible and how to prevent this condition. Refreshing the doctor and other medical staff's knowledge on this topic might increase their awareness and attention whenever they treat malaria patients, in order to prevent this potentially lethal complication of severe malaria.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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