

## Manifestations, Mismanagement and Diagnostic Challenges of Malaria and Typhoid Fever

Ijeoma Iheukwumere\*, Nwachukwu, Nkechi Chuks, Kanu and Anuli Mercy

Microbiology Department, Faculty of Biological & Physical Sciences, Abia State University, Uturu, Abia State, Nigeria

### Abstract

Malaria and typhoid are the recurrent infectious diseases with different etiological and vector agents in the endemic tropical regions of the world, yet, both infections display significant similarities in symptomological manifestations. Malaria is caused by a *Plasmodium* parasite transmitted by anopheles mosquitoes. It occurs mainly in the tropical regions of the world, while typhoid fever is caused by *Salmonella enterica* serotype *typhi*, and occurs worldwide. Nevertheless, both malaria and typhoid are known as the major causes of morbidity and mortality in endemic regions of world especially in the Indian subcontinent, Africa, Asia, or Latin America. The majority of malaria cases are found in countries where cost-effectiveness is an important factor and ease of diagnostic test performance and training of personnel are also major considerations. However, in Africa, it is endemic in the regions, south of the Sahara especially in West Africa. In Nigeria for example, malaria alone is one of the most persistent infections that adversely affect socioeconomic productivity and wellness of the population. What makes the coexistence of malaria and typhoid fever unique is the fact that they possess similar symptomology with multiple variable complication, yet, share the same pathological outcomes, which make sustained management and prevention difficult.

One of the major problems in managing malaria and typhoid fever in Nigeria for example, is the inherent problem of misdiagnosis and confusion in the physiological and behavioral manifestations of the two separate etiological infections. Both exhibit similarities in the signs and symptoms of the two diseases. Furthermore, most of the sufferers have the tendency to erroneously conclude that they have malaria when they have typhoid fever. Consequently, they resort to self-medication, which could put them at risk of more adverse outcomes. Some healthcare managers casually assume this erroneous diagnostic method and immediately prescribe malaria drug without proper investigation. The objective of this article is to review the scientific data from studies conducted in the tropics that provided information on malaria and typhoid fever infection in order to assess the challenges associated with diagnosis, manifestations and the management of these important infections in a view to have a better understanding on how to effectively control these infections.

**Keywords:** Symptomology; Misdiagnosis; Pathology

### Epidemiology of Malaria and Typhoid Fever

Malaria and Typhoid fever have been associated with poverty and underdevelopment with significant morbidity and mortality. Malaria remains the most complex and overwhelming health, facing humanity in vast majority of tropical and sub-tropical regions of the world, with 300 to 500 million cases and 2 to 3 million deaths per year [1]. About 90% of all malaria deaths in the world today occur in the sub-Sahara Africa and this is because majority of the infections are caused by *Plasmodium falciparum*, the most dangerous of the four human malaria parasites (*Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium vivax*, *Plasmodium malariae*), accounting for an estimated 1.4 to 2.6 million deaths per year in this region. In addition, the most effective malaria vector, *Anopheles gambiae* is the most wide spread in the region and the most difficult to control. In areas where malaria is highly endemic, a protective semi-immunity against *Plasmodium falciparum* is acquired during the first 10 – 15 years of life, and the majority of malaria-related morbidity and mortality happen in young children [2]. In contrast to that seen in the rich countries, typhoid fever remains an important cause of illness in the developing world. A recent epidemiologic study showed that south-east and south-central Asia are the regions of highest endemicity, North America and the rest of the developed world have low rates of disease [3-5].

The etiological agent of typhoid fever is *Salmonella enterica* sub-sp *enteric* serotype *typhi*. Typhoid fever is an important cause of morbidity in many regions of the world, with an estimated 12 to 33 million cases occurring annually. Cases are more likely to be seen in areas like India,

South and Central America, and Africa with rapid population growth, increased urbanization, and limited safe water, infrastructure, and health systems. It is estimated that there are more than 13 million cases occurring annually in Asia alone of which a large proportion occur during childhood, and in the wake of emerging multidrug-resistant strains of bacteria causing typhoid fever, the disorder is known to be associated with significant morbidity and mortality [2]. Typhoid fever represents the 4<sup>th</sup> most common cause of death in Pakistan [6]. Human beings are the only reservoir and host for typhoid fever and are transmitted by faecally contaminated water and food in endemic areas especially by carriers handling food. The disease has important socioeconomic impact because of the long recovery period [2].

### Common signs and symptoms

Although, malaria and typhoid fever have different etiologies, there seems to be a physiological convergence in the symptomatic

\*Corresponding author: Ijeoma Iheukwumere, Microbiology Department, Faculty of Biological & Physical Sciences, Abia State University, Uturu, Abia State, Nigeria, E-mail: [ijay2001kay@yahoo.com](mailto:ijay2001kay@yahoo.com)

Received August 27, 2013; Accepted October 14, 2013; Published October 21, 2013

Citation: Iheukwumere I, Nwachukwu, Chuks N, Kanu, Mercy A (2013) Manifestations, Mismanagement and Diagnostic Challenges of Malaria and Typhoid Fever. Malar Chemoth Cont Elimination 2: 109. doi: 10.4172/2090-2778.1000109

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patterns of onset. The predominant symptoms found in typhoid fever are headache, epigastric pain, nausea, and anorexia, together with fever from the afternoon to night, while the frequent complications are typhoid hepatitis, typhoid pneumonia, typhoid encephalopathy, intestinal haemorrhage [7]. Typhoid fever usually has higher than 39°C temperatures, which is the hallmark of the typhoid disease. Similarly, malaria shows closely very high body temperature (38-41.1°C) with similar signs and symptoms as found typhoid, albeit, with varying descriptive etiological peculiarities and definitions, such as typhoid hepatitis and malaria hepatitis; typhoid pneumonia and malaria pneumonia [4,7].

### The nature of fevers and outward manifestations

Although, malaria and typhoid fever share similar febrile characteristics, the number of people manifesting the signs and symptoms is higher in typhoid fever compared to malaria. However, in some instances, there exist a percentage of febrile patients without either of the etiological parasites readily detectable in the blood samples. This particular situation is an enigma, which is probably one of the contributory confusions in the accurate microbiological laboratory diagnosis of the two infections.

The usual classic findings of typhoid fever include rose spots, relative bradycardia, and stepwise fevers, but unfortunately, some of these signs are frequently absent [1] or could be found in other disease conditions such as measles and meningitis. Malaria onset on the other hand, is accompanied by profuse cold sweating, elevated temperature, tremor of the lips and extremities, and visual aura. Overall, structural paroxysms is obvious in malaria fever as against the stepwise pattern fever of typhoid fever, which is usually accompanied by severe headaches in typhoid fever as well as the presence of G.I.T. symptoms, which could be graded in consistency when compared to malaria [8,9].

Anemia and splenomegaly could be found in both disease infections but more pronounced in typhoid fever. Relatively, bradycardia as well as leucopenia is features of typhoid fever and not of malaria [9].

Consequently, using Widal test alone, one cannot differentiate typhoid fever from malaria. Malaria could interfere with serological diagnosis of typhoid and hence lead to misdiagnosis of typhoid fever [2,4,10-12]. However, it is of concern that poor diagnosis continues to hinder effective malaria and typhoid control in the tropics. This is due to a combination of factors, including non-specific clinical presentation of the diseases, high prevalence of asymptomatic infections in many areas, lack of resources and insufficient access to trained health care providers and health facilities, and widespread practice of self-treatment for clinically suspected malaria or typhoid fever [2].

The major management problems found in malaria and typhoid fever stem from the fact that they often occur in the same patient either at the same time or in sequence to each other [2,4]. Consequently, each marks the distinguishing features of the other with resultant adverse misdiagnosis effects. These misdiagnosis effects can be discussed under three pathological dimensions namely gastrointestinal tract manifestation, neurobehavioral manifestations, therapeutic drug resistance and side effects and undesired biochemical modifications of malaria and typhoid fever infections.

### Gastrointestinal Tract Manifestations

Gastrointestinal tract complaints are consistently found among patients that have typhoid fever. Intestinal bleeding in patients with typhoid fever usually occurs in the ileum. Gastrointestinal

manifestations may include diffuse abdominal pain, bleeding, perforation, cholecystitis and cholangitis. The diagnosis should therefore be suspected after collection of the appropriate clinical and travel history with confirmation by blood or bone marrow culture [1,12] showed, the most commonly involved area of the G.I.T. is the terminal ileum (100%), followed by the ileocecal valve (57%), the ascending colon (43%), and the transverse colon (29%). Left colon was intact in all cases. The most common colonoscopic findings include multiple variable-sized punched-out ulcers with slightly elevated margin, several edematous hyperemic mucosal patches with hemorrhagic spots or shallow erosions. Active bleeding was noticed only in one patient, who received endoscopic haemostasis twice. Intestinal bleeding in typhoid fever usually occurs from the ulcers in the ileum or proximal colon, and the most common colonoscopic manifestations are multiple variable-sized punched-out ulcerations [13,14] observed high fever, toxemia, constipation during first week of fever, complicated by encephalopathy and perforation during third week of typhoid fever is the typical manifestations of typhoid fever. Overall, the perforation of the ileum remains one of the commonest and the most dramatic complication of typhoid fever in developing countries where the infection is still prevalent [11].

### Neurobehavioral Manifestations

Neurobehavioral manifestations pathways of malaria infection have been reviewed elsewhere. These include neurophysiological impacts on the central nervous system through demyelination, immunohistochemical changes in the brain, and subsequent neuropsychological deficits. Consequently, malaria infection through these pathways may lead to deficits in growth, attention, memory, visuo-spatial skills, language, executive functions, and learning disabilities [15].

In addition, a self-limiting psychosis characterized by visual and auditory hallucinations and insomnia has been reported after mefloquine administration for presumed chloroquine resistant falciparum malaria [16].

Ferraro et al. [17] reported an unexpected cenesthetic hallucination-type neuropsychiatric side effect with hydrochloroquine (Plaquenil) in a patient treated for an erosive plantar lichen planus. Treatment with hydrochloroquine (400 mg/day) with topical corticosteroids and a short course of oral corticosteroids (0.5 mg/kg/day of methyl prednisolone) resulted in a short episode of temporo-spatial disorientation, followed by a feeling of depersonalization, cenesthetic hallucinations after 10 days of treatment. Chloroquine and hydrochloroquine may be at the origin of severe psychosis-like psychiatric side effects during treatment of malaria. The clinical presentation of the psychosis induced by synthetic anti-malarials is fairly homogeneous from one case to the next: onset in a patient without psychiatric past of manifestations such as delirium, hallucinations, maniac episodes or depression after an interval of a few hours to 40 days, usually regressing one week after suspension of the synthetic antimalarial [17]. In typhoid fever on the other hand, neuropsychiatric manifestations of typhoid fever are common in endemic areas, occurring in 18 of 40 consecutive patients at the University Hospital of the West Indies [18].

### Biochemical Changes due to Malaria and Typhoid Fever Infection

Malaria and typhoid fever have significant abnormal biochemical alterations, which play important role in the direction of the disease processes. In addition, these alterations have direct ripple effects on

the overall neuro physiological and behavioral attributes of other cells in the body [19] reported about typhoid fever pathogenesis which indicated the main clinical manifestations as:

- i. Bacterial type III protein secretion system.
- ii. The five virulence genes of *Salmonella* spp. that encoding Sips (Salmonella invasion protein) A, B, C, D and E, which are capable of induce apoptosis in macrophages.
- iii. The function of Toll R2 and Toll R4 receptors present in the macrophage surface (discovered in the *Drosophila*). The Toll family receptors are critical in the signaling mediated by LPS in macrophages in association with LBP and CD14.
- iv. The lines of immune defense between intestinal lumen and internal organs.
- v. The fundamental role of the endothelial cells in the inflammatory deviation from bloodstream into infected tissues by bacteria.

### Therapeutic Drug Resistance and Side Effects

In general, most of the drugs used in malaria and typhoid fever infections do what they are designed to do albeit, under appropriate physiological conditions. Unfortunately, combination and inappropriate drug use and self-medication raise a serious concern about the actual sources of drug resistance found in malaria and typhoid infections. Under these circumstances, it is difficult to determine whether the persistence of the infections after medication was related to plasmodia and salmonella defense mechanism or due to the host's errors in medication. In the light of this situation, therefore, meticulous monitoring of the outcomes and duration of each medication becomes imperative.

It must be added that in most Third World nations where malaria and typhoid fever are endemic, self-medication is prevalent and accepted as a norm. Most unqualified salesmen usually prescribe malaria or typhoid fever drugs without basic biochemical knowledge of the identity of the patient's infection. Such practices are amenable to inappropriate use of drug medication, and uncertainty about whether the persistence and resistance of the infections is due to ineffectiveness and inefficacy of the drug or are of disease origin [2].

### Laboratory Diagnostic Problems and Interpretation

The use of microbiological laboratory techniques is the most accurate and reliable method of diagnosis of malaria infection. The rapid diagnostic tests (RDTs) for malaria which use immunochromatographic methods to detect *Plasmodium*-specific antigens in a finger prick blood sample, can be performed in approximately 15minutes by individuals with minimal training, using test kits (available from several manufacturers) that require no electricity and special equipment. Compared to microscopy, the main disadvantages of currently available RDTs are: lack of sensitivity at low levels of parasitaemia; inability to differentiate between *P. vivax*, *P. ovale* and *P. malariae*, as well as between the sexual and asexual stages of the parasite; persistently positive tests (for some antigens) in spite of parasite clearance following chemotherapy; and relatively high cost per test. Other diagnostic methods are available, but they are neither suitable for wide field application nor for use in routine disease management and they include; microscopy using fluorochromes, polymerase chain reaction (PCR) based tests and antibody detection by serology [2].

Nevertheless, there exists the persistence of the "malaria manifestations" even after an appropriate drug treatment has been given

and a total elimination of the parasites from the blood stream of the infected persons is achieved. This could be as a result of over-diagnosis and mistreatment of malaria which results in other potentially serious infections being overlooked, such as pneumonia and invasive bacterial disease. Thus, resulting in adverse drug reactions and more wasteful of resources [20]. Consequently, a need for biochemical confirmatory test becomes mandatory to ensure reliability and accuracy of diagnosis. Malaria and typhoid fever can coexist and infect a single person at the same time. However, the facts that both malaria and typhoid fever display some similar symptomologies, reliability and accuracy of these confirmatory tests becomes confusing and compromised. It is very common practice for patients in many parts of the tropics, to undergo both typhoid and malarial treatment even when their diagnosis has not been confirmed [4].

One of the biochemical laboratory confirmatory tests often used in most endemic areas is the Widal Agglutination Test, which is used in some instances to differentiate malaria from typhoid fever. However, it has been found that a positive Widal agglutination test of a clinically diagnosed patient does not necessarily confirm a true *S.typhi* and *S. paratyphi* infections since other *enteric* bacteria as well as malaria parasites mimic both the 'O' and 'H' Salmonellae-antigens that form the core of Widal agglutination test kits [21].

Hence, it is suggested that the culturing of blood samples from all clinically suspected cases of typhoid and paratyphoid fever irrespective of the Widal agglutination antibody titer, should also require the necessity of performing malaria-parasite test particularly, in the malaria endemic regions of the globe, before proceeding on any antimicrobial therapy [21]. Therefore, exclusive reliance on serological diagnosis of this febrile disease alone could be misleading since there is a possibility of erroneous conclusions and treatment of typhoid fever based on single Widal agglutination test, whereas potential fatal illness such as malaria and other parasitaemia, non-typhoid salmonellosis, endocarditis and other gastro-intestinal infections may have been responsible [2,21]. Therefore, to exclude typhoid fever from malaria infection or vice versa, bacteriological and biochemical laboratory confirmation could be useful albeit, to greater extent under the prevailing infectious circumstances. Although, similar laboratory abnormalities could be found in both malaria and typhoid fever infections such as decreased leukocyte count, increased erythrocyte sedimentation rate, thrombocytopenia, and proteinuria using Widal test [8], the understanding of the comparative levels of these abnormalities could be useful too. Therefore, the relative levels of serological parameters used in laboratory diagnosis for both malaria and typhoid fever should be applied in order to achieve greater levels of diagnostic confidence in accuracy and precision.

### Distinguishing Features of Malaria and Typhoid Fever

Essentially, the distinguishing features between malaria and typhoid fever are given in Table 1. These distinguishing features are classified under differential criteria for simplicity. Although, both infections are pathophysiologically described as febrile in disposition, their respective complications are systemic and could be terminal. For example, while malaria has the propensity to damage and/or modify the structure of the blood and liver cells, typhoid fever attack mainly the gastrointestinal cells especially the cells of the ileal region of the gastrointestinal tract. Overall, typhoid fever has several uncommon manifestations with malaria. These include:

- i. Haematemesis as the presenting feature
- ii. Hepatocellular jaundice with hepatic encephalopathy

Differential diagnostic criteria	Malaria	Typhoid Fever	Comments
Enteric fever	16%	52.6%	31.4% cases unknown and classified as pyrexia [4].
Complication	Liver diseases	Intestinal hemorrhages and Ileum perforation	Both may lead to serious structural damage
Serum urea level, acidosis, jaundice, and peritoneal fluid higher	Relatively lower	Relatively higher	The severity in both cases depends on individual immune status
Fever mode	Paroxysmal	Stepwise pattern	These are definitively diagnostic
Headaches and G.I.T Symptoms	Very pronounced	Less pronounced	Could be persistent or intermittent
Anemia and splenomegaly	Same level	Same level	Depending on individual immune status
Bradycardia and leucopenia	Lower	Higher	It could be exacerbated by malaria presence
Response to 'O' and 'H' Salmonellae-antigens	Mimics	Does not mimic	Highlights the importance of confirmatory test to Widal agglutination test
Neurological and behavioral manifestations	Relatively high	Relatively moderate	Hallucination and dreamy
Causative agent	Plasmodia	Salmonella enterica serotype typhi.	The presence of Serum plasmodia in typhoid patients leads to diagnostic errors.

**Table 1:** Distinguishing features between malaria and typhoid fever.

iii. Acute intravascular haemolysis

iv. Probable disseminated intravascular coagulation. Haematemesis as the presenting feature in typhoid fever has not been reported previously [22] (Table 1).

## Clinical and Laboratory Management of Malaria and Typhoid Fever

### Clinical and laboratory management should include

Early diagnosis of severe malaria based upon a complete history, physical examination and blood smear/RDT for malaria parasites. Taking and reporting of blood smear and other investigations must not be allowed to delay treatment unduly.

- Provision of appropriate treatment with intra-venous Quinine or artemisinin combination therapy for patients diagnosed with *P. falciparum*.

- General management, nursing care and monitoring.

- Treatment of complications e.g. blood transfusion where appropriate.

- Treatment of hypoglycemia. Hypoglycemia remains a major problem in the management of severe malaria especially in young children and pregnant women. It should be deliberately looked for and treated accordingly.

- Laboratory investigations for other complications where indicated [7].

The definitive diagnosis of typhoid fever requires the isolation of *Salmonella enterica* serotype *typhi* from the patient [2]. Treatment of typhoid fever has been complicated by the development and rapid dissemination of typhoid organisms resistant to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol. In recent years, development of creeping resistance to fluoroquinolones has resulted in more challenges. Resistance patterns have led to a shift toward the third generation cephalosporins, azithromycin, and fluoroquinolones as empiric therapy for typhoid fever while awaiting the results of antimicrobial susceptibilities. Fluids and electrolytes may be given through a vein (intravenously). Malaria could be controlled through interventions to minimize human-vector contact while improved personal hygiene, targeted vaccinated campaigns and intensive community health education could help to prevent and control typhoid fever in the tropics [2].

## Conclusions

Distinguishing the onset malaria from typhoid fever infection has

been the major source of frequent misdiagnosis and mismanagement in Nigeria because of the similarities in the respective onset, symptoms, and modes of physiological manifestations. Hepatic manifestations are the dominant features of the illness in both infections. However, the ability of malaria and typhoid fever to simulate other common infectious diseases is a problem that should be investigated. It is recommended that appropriate confirmatory tests should be used whenever patients present with either malaria or typhoid fever in order to minimize the mix up between the two febrile conditions.

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