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University of Khartoum

Faculty of Medicine

Postgraduate Medical Studies Board

Neurological manifestations of *Falciparum malaria* in children above 6 years of age

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A thesis

submitted in partial fulfillment of the requirements for the

Clinical MD degree in Paediatrics and Child health

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1998

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قال الله تعالى :

(و قل رب زدني علماً)

صدق الله العظيم

سورة طه - الآية (114)

Dedication

To the soul of my father, soul of my mother,

To my brothers, sisters, my future candle Ahmed,

my first baby and his father

ACKNOWLEDGMENTS

Great thanks and thankful praises to the Almighty Allah for all the favours and guidance, he bestowed upon me throughout my life.

I am greatly indebted to my supervisor the late Prof. Awad Hassan Mahdi for constructive criticism throughout this study mayGod bless his soul.

I am indebted to Dr. A. Aziz Alamin, consultant paediatrician for his help in planning the protocol and initiation of this study.

I would like to express my thanks and gratitude to Dr. Salah A. Ibrahim and Dr. Elsir Hashim, consultant pediatricians for their continuous guidance, encouragement and much valuable advice.

My deepest gratitude extends as well to Dr. Salma Elbeely for her great help.

I also express my warmest thanks to the staff of the Central Laboratory (KTH), National Health Laboratory, and Ward 15 laboratory for their unlimited help in performing most of the investigations.

Great thanks to my patients and their families hoping them a better future life.

My great appreciation goes to the doctors in charge of my patients, and to the nursing staff for their co- operation.

A special message of gratitude to my sister Dr. Hafsa and my friend Dr. Amani A. Albeshir for their continuous moral and financial support.

I wish to express my special thanks to Mr. Mohamed Khalid for his participation in the data analysis.

Finally I am much indebted to Miss. Rehab H & Miss. Nawal for their great help in printing the manuscript.

List of Abbreviations

ACS	Adelaide coma scale
BCS	Blantyre coma scale
BCRR	Basic Case Reproduction Rate
CSF	Cerebrospinal Fluid
CPP	Cerebral perfusion pressure
EEG	Electroencephalograph
HB	Haemoglobin
HUVEC	Human umbilical vein endothelial cells
ICAM – 1	Intracellular adhesion molecule
ICP	Intra-cranial pressure
KCEH	Khartoum Children Emergency Hospital
MRI	Magnetic Resonance Imaging
ODC.	Oxygen Dissociation curve
P.F	*Plasmodium falciparum*
P. Oval	*Plasmodium Oval*
P. Malaria	*Plasmodium Malaria*
P. Vivax	*Plasmodium*
P. Knowles	*Plasmodium*
P. gallinaleum	*Plasmodium gallinaleum*
PCV	Packed cell volume
RSS	Random Blood Sugar
RIA	Radio immuno -Assay
TNF	Tumor necrosis factor
WHO	World health Organization

ABSTRACT

One hundred patients aged between 6 – 15 years suffered from neurological manifestations of *Plasmodium Falciparum malaria* and one hundred control with positive blood film but without neurological manifestations have been admitted in Khartoum Children Emergency Hospital (KCEH). The level of hemoglobin, packed cell volume, random blood sugar, blood film for malaria and the level of parasitaemia were done to all patients.

Fever, pallor, splenomegaly and hepatomegaly were the most important physical signs found in patients with neurological manifestations of malaria in the frequency of 85%, 43%, 52% and 47% respectively. Loss of consciousness was the commonest neurological manifestation found in [63%] of cases followed by convulsions [32%], hallucination [23%] and acute cerebeller ataxia [9%]. Weakness, aphasia and cranial nerve palsies were rare.

The commonest risk factors were deep coma [31%] repeated convulsions [24%], hypoglycemia [24%], and absent corneal reflex [13%]. There was a significant mortality rate in patients with neurological manifestations of plasmodium falciparum malaria [10%]. Neurological sequelae were reported in 18% of cases on discharge, in 10% after one month, and in 7% after 2 months.

ملخص الأطـروحة

في هذه الأطروحة تمت دراسة مائة حالة يتراوح العمر فيها ما بين 6 – 15 سنة تعـاني من أعراض دما غية نتيجة للإصابة بالملاريا الخبيثة (بلازموديم فالسبارم) و أيضا أضيفت مائة حالة أخرى أصيبت بالملاريا الخبيثة و لكن دون أي أعراض دما غية .

تمت الدراسة في مستشفي الخرطوم بحوادث الأطفال، و قد أجريت فحوصـات للمـائتين حالة تضمنت نسبة الهموقلوبين في الدم، نسبة السكر في الدم، وجود الملاريا الخبيثة فـي الـدم و كثافتها.

أهم الأعراض الإكلينيكية وجود الحمي، الأنيميا تضخم الطحال، و تضخم الكبـد و قـد و جدت نسبة 85%، 43%، 52%، و 47% تباعا و ذلك في حالات الإصابة الدماغية.

يعتبر فقدان الوعي أكثر الأعراض شيوعا حيث وجد فـي 63% مـن الحـالات و يليـه التشنجات و كانت نسبة 32%، و الهلوسة و كانت بنسبة 23%.أما الأعراض الأخرى فقد حدثت و لكن نسبة أقل كثيراً (الشلل النصفي ، فقدان القدرة علي الكلام).

من الملاحظ في الدراسة أن من أهم العوامل التي تساعد علي حدوث الأعراض الدماغية: حدوث الغيبوبية العميقة (أقل من 7، حسب مقياس جلاسكو للغيبوبة) و كانـت بنـسبة 31% ثـم التشنجات المتكررة و كانت بنسبة 24% و نقص السكر في الدم (اقل من 40ملمم/ لتر) و كانـت في 24% من الحالات.

نسبة الوفاة كانت كبيرة في حالات الإصابة الدماغية حيث كانت 10%.

و بقيت الأعراض الدماغية في 18% من الحالات عند الخروج من المستشفي. ثم تناقصت الي 10% بعد شهر المراجعة الأول، ثم إلى 7% بعد شهر المراجعة الثاني.

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INTRODUCTION AND LITERATURE REVIEW

1.1 History of Malaria:

Malaria has been known since antiquity Ebers, which mentioned fever and splenomegaly, documenting that the disease has been known since 1560 E. hypocrites described quotidian, tertian, and quartan fever with splenomegaly.[1]

Throughout history, swamps have been associated with fever. It was believed that malaria was brought by breathing bad air (mal = bad, aria = air). The elucidation of the parasitic etiology of the disease began in 1847, when Meckel observed black pigment granules in the blood and spleens of patients. In 1879, Fansten suggested that the granules caused the disease. [2]

For the following 30 years many studies on the etiology of malaria were done. Kelps in Germany and Tomes in Italy declared that the Bacillus malaria was the causative organism. A French physician named A.L. Laveran observed the pigment within the leukocytes and be saw clear bodies in the erythrocytes. C. Golgi differentiated between different species of plasmodia. [3]

In 1891 Romanovsky in Russia, developed a new method of staining blood smears based on methylene blue and eosin, and the mode of transmission however, remained unknown.

The idea " bad night air" remained popular for a long time. Patrick Manson was one of the first people to advocate the possibility of transmission by mosquitoes. In the night of the 16th August 1897 Major Ronald Ross dissected a female Anopheles mosquito and found pigmented spherical bodies in the wall of the insect's stomach, this was the first thread that lead him to elucidate the life- cycle of the plasmodium.(4) In 1962 Ronald Ross was awarded the Nobel Prize for his discovery. In 1938 James and Tare discovered exorythrocytic stages of *P. gallinaleum*, Short and Garnham demonstrated the exo-erthrocytic stage of *P. cynomongion* in monkeys and *P. vivax* in human.(5) In 1970s the WHO launched a global compaign to eradicate malaria. Unfortunately this program failed, and the WHO adapted the realistic policy of control rather than eradication of malaria. Today, malaria remains one of the most serious public health problems in the world wide.(6)

1.2 History of Malaria in the Sudan:

Malaria is one of the major public health and social problems in Sudan leading to high morbidity and mortality especially among younger children and pregnant women.

Malaria was very well known in Sudan and it was called (Wirdat Alkharief) i.e. the rainy season's fever, because most cases appear in the months following the rains.(7)

The intermittent pattern of malaria fever was observed by visitors to the Sudan and was recorded since 1865 along Atbara river, Bar Bar and Marawe.

In the year 1898, after the Battle of Omdurman and the defeat of the national army, malaria caused a lot of trouble to the foreign troops, and one third of the troops were affected. Next year in 1899 the conditions were the same and the mosquitoes were recognized as the causative agent and quinine was given as a prophylactic dose. In the year1905, the central sanitary board was established and was concerned with all matters concerning the questions of public health such as disease epidemics, and thus concerned with the situation of malaria in Khartoum and irrigation schemes.[8] The measures carried out by these programmers proved to be satisfactory under normal conditions, yet outbreaks continued to appear whenever high floods or heavy rains occurred as for example, the year from 1917 up to 1933 where epidemics of malaria were recorded all over the country.[8]

From the year 1939 onwards there was increasing incidence of malaria with peak levels in the years 1964 – 1966, 1970 and 1973 associated with a very high mortality rate. However, the number of cases reported would not reflect the actual number of malaria cases in the country, since these numbers represent only cases which presented to hospitals & health centers. In fact on the basis of the studies done by the statistic department of the Ministry of Health in the Sudan during the year 1977- 1983, the prevalence rates for

malaria per 1000 population in the different provinces of the Sudan were as follows: the Eastern Province took the lead in the prevalence of malaria infection, ranging from 144- 405 / 1000. then the rest of the regions had approximately equal prevalence rates of 126 – 173 / 1000. [9]

The year 1984 was an exception, as it was the year when the draught and desertification started. The level of the River Nile was very low at that time and the high incidence of fevers throughout the year and the year after were most probably the result of breeding of mosquitoes in the small pools formed by hoof prints left by animals coming to drink. The prevalence rate significantly rose from 144 in 1977 to 373 in 1993 & about 40% of out patient attendance was due to malaria. [7]

Malaria control program started in Sudan in early 1960s, with the aim of eradication. After evaluation, control rather than eradication was recommended & this was due to a technical (vector resistance to DDT), financial and administrative problem.[8]

The disease incidence is increasing remarkably due to an influx of refugees, immigrants and displaced persons, heavy rains and floods, the green revolution, new parasite strains and a chloroquine resistance problem and low socioeconomic status. Both the community & government recognize the threat of malaria. The National Comprehensive Strategy for the Sudan (1992-2001) stressed malaria control as a priority health policy. Hence, the Federal Government has constituted a Ministerial Committee

for Malaria Control, thus providing the highest political support for the issue. [9]

1.3 Epidemiology:

Malaria is widely distributed throughout the tropics except for the South, Central Pacific Islands. *P. falciparum* is the predominant species in the highly endemic areas of Africa, New Guinea, and Haiti, while *P. vivax* is more common in Central America and the rest of Asia.

P. malariae is widespread but often overlooked. In West Africa *P. ovale* largely replaces *P. vivax* to which the inhabitants are resistant. [10]

The epidemiological features of human malaria differ markedly even between endemic areas. At one extreme, as in West Africa, everyone is infected shortly after birth, parasitaemia is almost universal throughout childhood, and the brunt of mortality falls in early childhood.[11] By contrast, in parts of North India, malaria is a pandemic disease affecting all ages. These differences result from differing levels of malaria transmission affecting patterns of immunity in the human population.

The epidemiology of malaria is complex, but is relatively well understood. Climate and the ecology of the mosquito vectors are the primary determinants of malaria epidemiology. Transmission of the parasites is by a bite of the female anopheles mosquito. There is some variation of susceptibility to malaria within the anopheles, so that *P. falciparum* from

Africa may fail to develop in some European anopheles even under optimal condition.[12] Three characteristics of the anopheline mosquito density, man biting habit; and longevity are important in epidemiology. Mosquito density is the number of vectors present in one place. It is measured in relation to the human population rather than area. It was found that malaria transmission is proportional to mosquito density, the man – biting habit combines two features, the frequency with which the female mosquito feeds and the choice of host. A mosquito that feeds frequently will have a greater chance both picking up and passing on the parasite.[13] Malaria transmission is proportional to the square of the man- biting habit, because transmission involves both parasite uptake by bite and subsequent inoculation.[14]

Mosquito longevity has even greater effects. The duration of the extrinsic cycle, i.e. the interval between a mosquito ingesting infective gametocytes and the first day on which sporozoites are present in the salivary glands ready for transmission, depends on the temperature but will tend to be rarely less than 10 days. As mosquitoes of a given species have a relatively constant probability of dying regardless of age, the longevity may be described by the probability of surviving through one day and it varies greatly between mosquito species and environments. Thus the most effective transmission of malaria will be by a long – life mosquito which occurs at high density and frequently bites people. *A. gambiae* and A. crabbiness best fit this description.[13]

Malaria transmission is most conveniently measured in terms of basic case reproduction rate (BCRR). This is the average number of new cases of malaria, which will result from one human case of malaria in a place, before the case recovers, assuming all the other people are non-immune and uninfected. The BCRR may vary from over 1000 in some areas of America to below 1. The infection will not replace itself and the disease will die out. In the real world, the BCRR will vary considerably about a mean value. In areas with a very high BCRR every one will become infected. The variation will be immaterial and the amount of malaria seen will be determined by acquired immunity in human. This is the situation called stable malaria and is seen in sub-Saharan Africa and New Guinea particularly.(14) Because the BCRR is so high, central methods are used aiming to break transmission here to reduce BCRR by a factor of perhaps 1000 to bring it below 1. By contrast, in places where the BCRR is say,3, natural variations will cause the BCRR to be below l for most of the time. There will be intermittent periods of transmission, and epidemics will occur from time to time. This is called unstable malaria. Because human immunity will be much less, people of all ages will get ill during the epidemics, but transmission will be much easier to control. (15)

Even in stable malaria areas, seasonal variation may occur. In the African savannah, no mosquitoes may be biting during the hot dry season, and in more temperate zones it may be too cold for transmission for part of the year, still the annual peaks will be comparable with all children infected

each year. While the division between stable and unstable malaria is the most useful, an earlier classification of areas by the parasite prevalence in children or by proportion of children aged 2-9 years with splenic enlargement gives a better cumulative picture of the number of malaria attacks than does the parasite prevalence which is influenced by causal chemotherapy.[16]The epidemiological background to clinical malaria is not steady. The wide spread availability of chloroquine and other effective chemotherapy in endemic areas has resulted in early treatment of a proportion of infections. This often leads to disparities between a high spleen rate in children and an artificially low parasite rate. With increasing use of chemotherapy the acquisition of immunity is deferred and the range of age at which cerebral malaria is seen may increase. [17]

1.4 Epidemiology of malaria in the Sudan:

Population movements play a major role in the Epidemiology of malaria. The annual influx of labour from Kordofan, Darfur and the temporary cotton- pickers, cause an outstanding effect on malaria epidemiology in the Sudan.[7]

The Sudan medical service during the period 1955-1965 showed that *P. falciparum* is by far the most frequent species constituting more than 90% of the infections encountered. *P. vivax* and *P. malariae* occur in about 5- 10% of infections, but *P. ovale* is not found in the Sudan. In 1986 it was showed

that *P. falciparum* was the only parasite seen in Northern Sudan, while in Southern Sudan the pattern was 84.4% *P. falciparum*, 8.53% *P. vivax*, 6.8% *P. malaria* and 0.15% *P. ovale*. In Eastern Sudan p. vivax is encountered but *P. falciparum* was the main malaria parasite. [9]

Anopheles (A) Gambia and Anopheles Funestus which have a high vectoral potential and a wide distinction were the only confirmed vectors of malaria in the Sudan. A: Gambia is most dangerous and wide spread vector of malaria and act as a rainy season vector. Secondly comes the vector A. Funestus, which is found predominantly in central and Southern Sudan. It is largely responsible for a second wave of transmission during the dry season.[1]

Temperature, relative humidity, the rain falls, the rise and fall of the Nile and the irrigation system tend to vary with the distribution of the vector, and hence the disease occurrence. Therefore the whole country can be considered as an endemic zone. The Northern parts, along the Nile and its tributaries are hypo-endemic, where less than 10% of the population are affected. The desert zone is malaria free. In central Sudan, the disease is mainly meso-endemic, where between 11-50% of the population are affected.[7]

The determinate factor to malaria transmission in the North is the Nile level. A. Gambia is limited to the river bed in the remaining pools created by receding floods especially in the months of November to June. [8]

In the Gezira irrigated scheme and irrigated parts of Southern Blue Nile Province, the main transmission season commences shortly after the beginning of the rains and emends approximately one month after they have ceased (May to October). This is followed by another wave of transmission during the irrigation and cotton- picking season (October- January).[9] In the non-irrigated, non riverian parts of central Sudan, malaria transmission coincides with the rainy season. In the Southern Sudan because the climatic conditions favor the longevity of vectors and mosquito breeding places are available all the year, malaria transmission is of high degree of stability. In the savannah belt of central Sudan, where the conditions are just suitable for maintenance of *A. gambia*. There is a gross fluctuation of malaria, which depends on the relative humidity and abundance of rainfalls in the areas concerned. [8]

1 .5 Malaria Parasitology:

Malaria is not only the most important parasitic disease of human, with a global incidence of malaria today of around 200 million cases per year with over a million deaths, it has also had the largest effects on the course of history and settlement in tropical regions.[18]

In recent years it has been the subject of massive control efforts which have had varying degrees of success, and the disease has increased again in the last two decades. The recent history of health care in the third world can only be understood in the light of malaria eradication program. The role of

malaria as the pre-eminent tropical disease is thus well deserved, and the problems of both treatment and control today are more complex and intractable than ever before.[19]

Whereas there are over a hundred species of malaria parasite (Plasmodium), there are only four species which have humans as their natural vertebrate host. These are *P. falciparum*, *P. malaria*, *P. vivax*, and *P. ovale*.[20]

Each of the human malaria species have biological, morphological, and clinical characteristics which distinguish them from each other.

Developmental characteristics of human malaria parasites:

Species	***F. falciparum***	***P. vivax***	***P. ovale***	***P. malariae***
- Prepatent * period	8-25 days	8-27 days	9-17 days	15– 30 days
- Length of sexual erythocytic cycle	48 hrs.	48 hrs.	48 hrs.	72 hrs.
- Red cells parasitized	All	Reticulocytes	Reticulocytes	Malure erythrocytes
- Merozoites per schizont	8- 32	12- 24	4- 16	6- 1

- Relapse forms	No	Yes	Yes	No, but persistent red cell infection up to 30 years
- Drug resistance	Yes	No	No	No

* Time from ineffective mosquito bite to appearance of parasites. [21]

Despite these differences, the overall biology of the life-cycle is similar for the various species.

In both the mosquito and mammalian hosts the life-cycle of plasmodium species can be seen to consist alternatively of invasive stages and of stages capable of intracellular asexual division. There is also asexual stage of the life cycle which by facilitating the exchange of genetic information between parasitic strains or genotypes, assists in the generation of genetic diversity within the parasitic population.[22]

Infection is initiated when sporozoites from the salivary glands of female Anopheles mosquito are inoculated during a blood meal into the human blood stream. How these organisms target and invade hepatic parenchyma cells is still unclear. The process is extremely rapid, probably commencing within a few minutes and being largely complete with in 30 minutes. Entry into the hepatocyte may be direct or may possibly occur after

passage of the parasite through kupfer cells. Once inside the liver cell, two alternative pathways of differentiation are possible.[23] In all species the parasites initiate intracellular asexual multiplication. However, in addition, in *P. vivax* and *P. ovale* infections a proportion of them enter a cryptobiotic phase in which they are termed hypnozoites. These may lie dormant for months or even years[24] before starting to divide, thus being responsible for the late relapses characteristic of infections. In *P. falciparum* and *P. malaria* infections there is no cryptobiotic phase and therefore relapses from the liver do not occur. Never the less both of these infections are of chronic nature and blood infections may persist for a few years in the case of *P. falciparum* or decades in the case of *P. malaria*.[25]

Once initiated, the time required to complete the intrahepatic multiplication is again depending on the parasite species. The products of the liver stage (the extra-eryrothocytic merozoites) are liberated in their thousands form each parenchymal cell into the blood stream. Here they attach to and invade circulating erythrocytes. Inside the erythrocyte, asexual division commences and over a period of 48 hours *P. falciparum*, *P. vivax*, *P. ovale* or 72 hours (*P. malariae*), the parasites develop through a well defined series of morphological changes from ring to trophozoite.[26] These are liberated by red cell lysis and immediately invade uninfected erythrocytes producing a repetitive cycle of invasion and multiplication. Because the intra-erythrocytes division cycle is in general synchronous (particularly in *P. vivax*

and *P. ovale* infections) and also tied to the diurnal cycle of the host, erythrocyte lysis and merozoites release occur at approximately the same time of day for the duration of the infection for a given individual. The concomitant release of pyrogens is responsible for the periodic “agues” which have long been a diagnostic feature of malaria infection and which occur at the time of merozoites release. The asexual blood forms are the only forms of the parasite which give rise to clinical symptoms and signs of malaria.[27]

1.6 Pathogenesis of *Plasmodium falciparum* malaria:

Random collision between merozoites and erythrocytes results in the attachment of the parasite at any point on its surface to the red cell, this event is mediated by an extremely specific interaction between molecules exposed on the surface of the invading merozoites and the target erythrocyte. [28]

As a result of its entry and growth within the erythrocyte, the parasite produces a number of changes in the red cells. These may be summarized as follows:

1) Degradation of soluble red cell proteins mainly hemoglobin.

2) Changes in erythrocyte size, shape and deformability.

3) Alteration in the transport proportion of the erythrocyte membrane.

4) Association of parasite – derived proteins with the internal surface of the eryhrocyte membrane known as “knobs”. [29,30,31]

Late asexual stages of *P. falciparum* are absent from the peripheral circulation by virtue of their sequestration and by capillary endothelium.

The major clinical manifestations of malaria may be attributed to two general factors: (1) the host inflammatory response which produces the characteristic chills and fever as well as other related phenomena, (2) anaemia arising from the enormous destruction of erythrocytes.[32]

The host inflammatory response was observed by Macpherson and others, in severely ill *P. knowles*; infected rhesus monkeys, where they noted an increase in vascular permeability to labeled albumin and insured penetration of the brain by water-soluble dyes. The factors responsible for this were considered to be kinins and the increased permeability was reversed rapidly by hydrocortisone and chloroquine, but the clinical manifestations and the main pathological findings e.g. infiltration, little or no sequestration are different from those of human malaria.[33]

The rapid development of shock in severe malaria is termed algid malaria and is one of the observations of inflammatory response in the gastrointestinal tract, characterized by nausea, vomiting, abdominal pain, and watery diarrhoea.[34]

Shock may result from stress-induced gastrointestinal bleeding (i.e. hypovolemia), severe hypoxaemia and acidosis or gram-negative septicemia. Spontaneous bacterial septicemia can cause sudden clinical deterioration in severe *falciparum malaria*.[35]

Anaemia results form a combination of parasite destruction at schizogeny, accelerated removal of unparasitized erythrocytes and ineffective erythropoesis.[36]

As a result of anaemia the oxygen carrying delivery will be reduced. In order to maintain oxygen delivery blood flow increases and the haemoglobin oxygen dissociation curve (ODC) is shifted to the right causing an increased unloading of oxygen at the tissues.

The number of red blood cells lost by parasite destruction is underestimated from the peripheral blood film because of the unknown number of sequestered cells.[37]

In acute malaria there is accelerated destruction of unparasitized erythrocytes associated with increased splenic clearance. This was confirmed by Soni and Cox working in *P. gallinaleum* infected children where they found that a large number of non parasitized red cells were lysed and suggested that they may be opsonized for phagocytosis or complement – mediated haemolysis may be facilitated. Reduced survival of unparasitized erythrocytes has been documented both in acute malaria and following treatment .[38]

This may be associated with structural alterations of non-parasitized immature and mature red blood cells. The rate of abnormal red blood cells correlated with the degree of parasitaemia.

Massive haemolysis of red blood cells may lead to various complications in functions of different organs such as increased serum bilirubin. When its concentration is very high, this may indicate hepatocyte dysfunction. However, jaundice is common in adult patients but uncommon in African children).[39]

Some patients present with "Black water fever" which begins with rigors and fever followed by massive intravascular haemolysis, haemoglobinuria, collapse and often acute renal failure and uremia. The pathological findings in the kidney are necrosis of tubules and occasionally haemoglobin casts. In many patients parasitaemia is absent at the time when haemolysis occurs. Haemoglobin itself is not nephrotoxic in well hydrated animals and humans. Many patients with haemoglobinuria do not develop renal failure, but other compounds released from lysed erythrocytes can induce active tubular necrosis, especially in the presence of dehydration and acidosis.[40,41,42]

Endocapillary proliferative glomerulonephritis was the major pathological change observed in squirrel monkeys with acute *P. falciparum* infection.[43]

The peroxides anti-peroxides method demonstrated the presence of IgG, IgM, and *P. falciparum* antigens in the mesangial and basement membrane. These findings were consistent with those seen in humans with acute *P. falciparum* infection .[44]

Malaria pigment is taken up by circulating leukocytes and is deposited in the reticulondothelial system. In severe cases the viscera especially the liver, spleen, and brain become blackish as the result of pigment deposition.[45]

Cerebral malaria, the most important complication of falciparum malaria is an asymmetric encephelopathy that presents as unarousable coma, convulsions occurring in half of all adults and majority of children. The manifestations of pathogenesis of cerebral malaria is not definitely known. However, two possibilities are (i)mechanical abnormalities (ii) immune pathology. In a study vascular and metabolic abnormalities performed in 11 cases of post cerebral malaria stroke, four cases showed large vessel obstruction and one segmental narrowing. The remaining six cases were normal. [46]

The “mechanical” hypothesis for cerebral malaria is provided by evidence of cerebral anaerobic glycolysis associated with inadequate oxygen delivery to the brain consistent with either inhibition of cerebral oxidative metabolism or the microcirculatory hemorrhage and cerebral endothelial cell

damage. This damage is presumably one of the causes of the break down of the blood- brain barrier. [47]

The immuno-pathological factors are by the deposition of the knobs-protein antibodies which were observed in the basement membrane of cerebral capillaries. This result indicates involvement of knobs protein deposition in the pathogenesis of cerebral malaria. In the studies by Boonpucknavig only three of the six fatal cases had parasitized erythrocytes in the cerebral microvasculature. These findings are interpreted as representing immune damage. [48]

Retinal hemorrhages are also commonly seen in cerebral malaria.

1.7 Pathophysiology of *Plasmodium falciparum* malaria:

Plasmodium falciparum malaria is the most important parasitic disease of man. It has stimulated a considerable amount of scientific and medical research.

Since the review by Maeraith and Flecher in 1972" our understanding of pathophysiological mechanisms in malaria has advanced considerably in areas such as the pathogenesis of metabolic dysfunction, the molecular processes involved in cytoadherence, and the cause of anaemia. However, in other areas progress has been slow.[49]

In severe *P. falciparum* malaria there is a greater parasite load and sequestration in the microcirculation of the vital organs. These two factors account for the lethal potential of this parasite.[50]

The greater parasite load may be from repeated infections leading to anaemia, debility, and macrophage and T cell- mediated immuno suppression. These manifestations enhance parasite multiplication.[51]

1.7.1 Sequestration:

The peripheral blood in *P. falciparum* malaria rarely contains pigmented trophozoite and schizonts. The intravascular sequestration of erythrocytes containing these mature forms of the parasite is an essential pathophysiological feature of the *P. falciparum* malaria.[52] The degree of vascular sequestration varies in the different organs, being greatest in the brain in patients with cerebral malaria, and least in the skin.

In patients who die without developing cerebral malaria, sequestration are significantly less in the brain. These findings suggest a relationship between the organ distribution of sequestration and pathology[53]

1.7.2 Cytoadherence:

The principal event causing sequestration and impeding microcirculatory flow appears to be cytoadherence of parasitized erythrocytes to vascular endothelium. Cytoadherence is a specific process in that it occurs only in capillaries and post capillary venules, and involves only erythrocytes containing the more mature stages of the parasite (trophozoite and

schizonts).[54] The cytoadherence properties of p. falciparum appears to be modulated by the spleen. It is not known how this modulation takes place. All at the ultra-structural level election, dense knobs form on the erythrocyte membrane and are seen at the point of contact between the parasitized erythrocytes and endothelial cells. These knobs were considered essential for cytoadherence by facilitating the initial attachment of the infected erythrocyte to the vascular endothelial cell. [55,56]

1.7.3 Perturbations of cerebral hemodynamics:

The mechanism of death and neurologic sequelae in Africa children with cerebral malaria are undetermined. Because pathologic features are confined to the cerebral vascualture, perturbations in cerebral hemodynamics may be responsible. In comparing the transcranial Doppler findings in 50 children with cerebral malaria with those of 115 conscious Kenyan children, cerebral blood flow velocity was increased in the first group. In addition, 10 children with cerebral malaria were studied during the agonal stages. In the children with cerebral malaria, cerebral blood flow velocity was increased in 30%, usually associated with seizures. Of the 11 children who developed neurologic sequelae, six had sonographic abnormalities associated with lateralizing deficits, including four children with hemiparesis (in two children the contra-lateral middle cerebral artery could not be insonated and two had transient increase in blood flow velocity associated with seizures).[57] In the children with severe intracranial hypertension there was a significant linear

relationship between the cerebral perfusion pressure and blood flow velocity, suggesting that auto-regulation was impaired. Sonographic features of progressive intracranial hypertension were observed in three children with cerebral malaria who died. Perturbations of cerebral hemodynamics are associated with a poor outcome in kenyan children with cerebral malaria.

This research began with the observation that parasitized erythrocytes adhere to cultured human umbilical vein endothelial cells (HUVEC) in vitro with the same stage and host all specificity as observed with sequestration in vivo.[58]

There was no significant difference in HUVEC between isolates obtained from mild or severe cases.

Under investigation, are the receptors of cytoadherence thrombospondin which were identified as potential receptors produced by activated platelets. The second molecule was leukocyte differentiation antigen (D36 a membrane glycoprotein . The molecule, the intracellular adhesion molecule (ICAM-1) or (CD54) has been identified by David 1988.[59]

1.7.4 Rosetting:

Non-parasitized erythrocytes were observed to agglutinate around red cell containing mature stages of the parasite in vitro. This phenomenon is termed rosetting and may some times be seen in fresh blood samples. [60,61]

Rosetting occurs only with species of plasmodium, which also exhibit cytoadherence. These phenomena occur with mature stages of p. falciparum and begin often approximately 26h of intraerythrocytic development.[62]

1.7.5 Cytokines:

In acute infection, invading organisms or substances derived from them stimulate host mononuclear cells to release a variety of polypeptides known collectively as Cytokines. These are believed to have a role in the pathogenesis of many of the clinical manifestations of infection. [63]

Tumour necrosis factor TNF is acytokine, suggesting the possibility that it may mediate some of the clinical features and complications of *P. falciparum* malaria.[64] Also, TNF may have a role in the Pathophysiology of *P. falciparum* malaria such as adhesive properties to endothelial cells and leukocytes, and it is possible that circulating or locally generated TNF may accelerate the cytoadherence of parasitized red cell to cerebral venular endothelium that result in sequestration. [65]

The parasitized erythrocytes have difficulty in transfusing the capillary bed and, as a result, blood flow obstruction occurs leading to dysfunction in the organ, such as ischaemia, hypoxia and any toxic effect resulting from release of unidentified materials from the “sludge”.[51]

Obstruction of large vessels may occur rarely in childhood cerebral malaria leading to stroke.

Ultra-structural studies of parasitized erythrocytes have shown that these infected cells are less deformable than normal cells, and might therefore not pass as easily throughout capillary. However reduced erythrocytes deformability alone does not explain the phenomenon of sequestration and does not explain the concentration of parasitized erythrocytes in venules which are down stream.(63)

1.8 Human Malaria and Immunity:

The appearance of the symptoms of the disease, when humans are exposed to infection with *P. falciparum* malaria depends on several factors, including the environmental factors, location, parasite circulence, as well as other factors depending on human intrinsic characters such as age, pregnancy and immune response.(64)

Age may be an independent factor, i.e. for the same exposure, adults develop immunity more rapidly than do children. In areas where transmission is unstable (seasonable), then symptomatic disease is seen at all ages. The principal manifestation of severe malaria in these circumstances is cerebral malaria, whereas severe anaemia in young children is more prominent in areas of intense stable transmission. (65,66)

Malaria parasites exhibit considerable antigenic diversity, and readily undergo antigenic variation, the host immune system is actived in a non-specific manner while malaria antigen-specific immune response is

suppressed. The importance of the immune system in controlling and eradicating parasite can hardly be exaggerated. (67)

The evidence of immune deficiency was until recently not been compelling, mainly because immunologically crippling disease tending to escape attention in endemic areas. The information coming in, already indicates that this form of immune deficiency is highly permissive for growth of intracellular protozoon parasite. (68)

Acute malaria is associated with both activation and suppression of the immune system. The development of immunity in children infected with *P. falciparum* is though to be related to their immunologic response to certain soluble parasite – derived exo-antigens. Antibodies to *P. falciparum* ring stage surface antigen (RESA) may be import for controlling parasitaemia. (69) There was a slow increase in antibodies prevalence and concentration with age that continued to occur even to the age of 40 years. There is no correlation between immune response and morbidity indicators. There is no correlation between immune response and morbidity indicators. The serum level of IgM and IgB were significantly increased in adults compared with children aged 3 – 15 years. This may confirm the slow development of immune response. (70)

Neutrophils and macrophages can ingest free merozoites, and infected erythrocytes commonly contain malaria pigment. In vitro, neutrophils can be

shown to be activated by co-incubation with malaria parasites and that they can kill malaria trophozoite and schizonts .[71]

The mechanism of the immune suppression in acute *P. falciparum* malaria is complex. A defect in production of IL2 and IL-2 receptor expression in response to malaria – specific antigen has been demonstrated. The load of blood – stage parasites may be one factor that exerts an immunosuppression effect on the antibodies response to the sporozoites. [72]

The spleen plays a central role in the clearance of parasitized erythrocytes, recognizing their loss of deformability and opsonization with antibodies and / or complement components. In acute *P. falciparum* malaria removal was increased in patients with splenomegaly, whereas parasitaemia was found to have a significant influence on lymphoprolifrative and antibody response to the exo-antigens of infected erythrocytes.[73]

1.9 Clinical Features of Falciparum Malaria in Children:

In areas of intense transmission *P. falciparum* malaria is considered to be the most important cause of morbidity and mortality in children aged between 1 and 5 years. A study conducted among admitted children in Burkina Faso showed that (28.7%) of the cases were due to malaria compared to (16.8%) case due to respiratory tract infection.[27]

The symptoms occur rarely in first month of life for a variety of reasons, which include the passive immunity from mother and high

haemoglobin F. content, severe disease is rare in this age. Most deaths occur in age group 1 – 4 years. (74)

In children the classical feature of the malarial paroxysms are not seen. The infection is usually very severe in non immune children. The picture varies according to the degree of immunity, chemprophylaxis, or partial chemotherapy.(75)

None of the clinical features of malaria is diagnostic since pattern and intensity vary with age, state of immunity, general health, and nutritional status of the patient. Several days of prodromal symptoms such as malaise, headache, myalgia, anorexia, fever, vomiting and convulsions may occur.

The most important complication of *P. falciparum* infection in children are cerebral malaria with repeated convulsions and severe anaemia (Hb < 5.0 gm/dl haematocnt < 20%). The mortality of cerebral malaria in children is 10 – 40%. Most deaths in children admitted to hospital occur within the first 24 hours of admission.(3) Other complications of P. F. malaria occur in children but are less common than adult.(77)

1.9.1 Cerebral Malaria in Children:

Cerebral malaria is defined as a state of unarousable coma not attributable to any other cause in a patient with falciparum malaria e.g. Hypoglycaemia and transient postictal coma. The degree of unconsciousness should be assessed by Glasgow coma scale in children more than 5 years, and modified Glasgow coma scale such as Blantyre coma scale should be used for

children less than 5 years.[78] The child is usually febrile, Core (rectal) temperature is more reliable than oral or axillary measurements. Jaundice and pallor are common. The patient looks severely ill, often anaemic and jaundice with moderate tender enlargement of the spleen and liver. Useful negative findings are the lack of lympadenopathy and rash (apart from herpes febrilis). Skin and the heart may reveal flow murmur Cardiac output may be very high because of fever, anaemia and peripheral vasodilatation. Tachypnoea may also result from fever or may indicate pulmonary oedema, aspiration pneumonia or metabolic acidosis.[79] Papliedema is very rare but retinal haemorrhges are common. The pupils are normal. Disorders of conjugate gaze are very common presented as divergent eyes. Muscle tone and tendon reflex may be normal, decreased or increased. Ankle and sometimes patellar clonus may be elicited and the planter reflexes are invariably absent. decerebrate and decorticate postures and opithotonus may occur especially in patients who are hypoglycaemic.[80] High fever alone can impair cerebral function causing delirium, confusion, irritability, psychosis, and convulsions. In Thai adults, the coma of cerebral malaria is more prolonged than in African children, and there is higher incidence of acute renal failure, jaundice, and pulmonary oedema.[81] Studies in the Gambia and Malawi found that 26-32% of children with severe malaria were hypoglycaemic. Only 1 of 19 hypoglycaemic children in Malawi responded to intravenous dextrose, suggesting that underling cerebral malaria was also presents. About half the

patients with cerebral malaria have generalized convulsions. Self-limiting psychosis was reported in 2 children 4 to 5 days after recovery from cerebral malaria coma. It was characterized by visual and auditory hallucination with or without aggressive behavior. Some patients show neurological sequelae. These include cranial nerve lesions, acute cerebeller ataxia, transient – psychosis, cortical blindness, muscle tone disorder, aphasia with incidence of 6 to 12 %.[81]

Anaemia is an inevitable consequence of all but the mildest infections. It is more severe in patients with high parasitaemia, schizontaemia, secondary bacterial infection, and renal failure Jaundice is present but is rarely associated with biochemical evidence of severe hepatic dysfunction.[23] Hypoglycaemia is being recognized increasingly in patients with malaria. Patients with severe or uncomplicated falciparum become hypoglycaemic from a few hours to 6 days after quinine.[82] Pregnant women and children with malaria and other patients with hyperparasitaemia become hypoglycaemic without quinine therapy .[80,83]

The symptoms and signs of hypoglycemia, such as anxiety, breathlessness, confusion, sweating, restlessness, fatal bradycardia, coma, and extensor posturing may be misinterpreted as merely manifestations of malaria. Hypoglycaemia in children usually occurs in the pre-treatment period, with appositely, decreased circulating insulin, and commonly occur in

any severe infection, and is an important problem in malnourished children. Pulmonary oedma is rare in children.[84]

Prolonged, multiple seizures complicate a high proportion of cases of childhood cerebral malaria. It can present as an episode of status epilepticus, partial motor, generalized tonic-clonic and partial with secondary generalization. Some children present with subtle seizures. Several studies showed an association between convulsions and neurological sequelae, and they are considered as an important part in the pathogenesis of coma in childhood cerebral malaria and are likely to contribute to both the morbidity and mortality of this disease.[85] All forms of cerebral dysfunction in malaria including repeated convulsions, should be managed as being clinical manifestation of cerebral malaria .[86]

As regard to immunological findings, they are partly variable among different age groups. Infants in endemic areas usually have mild disease with low grade parasitaemia, probably because of passive immunity acquired from immune mothers. [66]

The parasitaemia rate increase with age, from 0-10% during the first three months of life to 80-9-% by one of age. By school age, a considerable degree of immunity has been developed and serum level of IgM and IgG were significantly increased in adults group than children. In children, antibodies prevalence was associated with both the presence of the parasite and an enlarged spleen. The prevalence of asymptomatic parasitaemia

associated with a high level of C4 may play a protective role in asymptomatic malaria in children. In areas of low endemicity however where the immunity in the indigenous population is low, severe infection occur in all age group including adults.[70]

Cold periphery, deep coma, and hypoglycemia following childhood cerebral malaria were the clinical signs and laboratory parameters that predicted death most strongly. [87] More than 90% of the children with elevated urea levels on admission, or those who experienced multiple episodes of hypoglycemia or multiple convulsions subsequently, are more likely to die.[88] These combination of clinical and laboratory abnormalities can identify a group of children with cerebral malaria who are most at risk of dying, who require intensive care and who are candidates for new forms of therapy . In view of the short time interval between admission and death in many children, emphasis must be placed on the prevention or early recognition or investigation of the cause and treatment of acidosis in the distinct health clinic as well as the central hospital.[89]

1.9.2 Neurological sequelae following malaria falciparum infection:

The definition of severe malaria is no longer limited to cerebral malaria but is as well extended to other clinical forms of the disease.

Interesting work done in Togo regard the epidemiological, clinical and evaluative aspects of severe malaria. This study included 549 children, aged form 0 - 15 years, hospitalized in 1994 – 5 in the pediatric department of the

Lome – Tokoin University teaching hospital for severe malaria as defined by World Health Organization (WHO) criteria.[90] The hospitalization frequency was 7.44 %; the maximum frequency was from 1 – 5 years of age, but 6.56 % of patients were more than 10 years old. The most frequent clinical form was that of severe anemia, followed by cerebral complications, as seen in many African countries. The death rate was 18.94 % and the proportional morality was 8.21 %; 2.73 % of the patients had neurological sequelae (behavior disturbances in five cases, aphasia in four, hemiplegia in three, mumbling in one, oculomotor paralysis in one, and cerebellar ataxia in one). Hypoglycemia was fairly frequent (11.6%) and was associated with a poor prognosis. It is possible to improve severe malaria prognosis in Africa by insisting not only on better equipment in intensive care wards, but also on improved and early management of hypoglycemia the patterns of neurological sequelae of childhood cerebral malaria among survivors. In caliber, Nigeria, all patients received intravenous quinine infusion and supportive care.[91] Survivors were followed up until detected neurological sequelae had resolved, the case fatality rate was 13.3 %. Eleven (28.2%) of the survivors developed neurological sequelae. [92]

Prolonged coma, focal seizure and abnormal posturing decorticate/decerebrate) were associated with increased risk of sequelae. Commonest neurological sequelae were cortical blindness (3/11), speech disorders 3/11 : aphasia or echocalia (and motor abnormalities 5/11:

dyskinesia hemiplegia). Eight cases recovered completely from the neurological deficits within a mean period of three weeks. One persisted with hyperactivity and attention deficit, and had remarkable improvement at the sixth month of follow up but developed secondary dyslexia and other learning disabilities by the third year of follow up. Although short lived, neurological sequelae of C M appear common among these Nigerian children, early diagnosis, use of appropriate drugs and large scale malaria programs can prevent malady.[93]

In a prospective hospital based study in north India, malaria accounted for 1.5% of paediatrics out patient attendance during 1 year. A marked increases in the prevalence of malaria was noted during the post moon months. *Plasmodium falciparum* was the causative species in 44.4% of cases, in contrary to previous reports of low prevalence of this parasite in the area. Pyrexia with or without chills or rigor, vomiting, pallor and hepatosplenomegaly were the common presenting clinical features. Splenic and hepatic enlargement were seen more frequently with *P. vivax* than *P. falciparum* infection [P less than 0.001 and [P less than 0.01, respectively]. Convulsions were present in 20 % of cases. [94]

Out of 604 Gambian children admitted with falciparum malaria to one hospital between September and December 1988, 308 had cerebral malaria and 203 were severely anaemic with haemoglobin less than 6g (14.4 %) of those with cerebral malaria died, as did 7.8% of those with severe anaemia.

32 (12%) of children surviving cerebral malaria had residual neurological deficit. 69 other children were admitted with clinical features strongly suggestive of cerebral malaria, but with negative blood films. Sixteen of those died and 3 had residual, neurological deficits. The commonest sequelae of cerebral malaria were hemiplegia (23 cases), cortical blindness, aphasia and ataxia.[95] Factors predisposing to sequelae included prolonged coma, protracted convulsions, severe anaemia, and biphasic clinical course characterized by recurrent recovery of consciousness, followed by recurrent convulsions and coma. At follow up 1–6 months later, over half of these children had made full recovery, but a quarter were left with a major residual neurological handicap in the tropics.[96]

Over a period of months, 109 patients were admitted to the medical wards of the Gondar college hospital with malaria. Out of these, 26 patients (24.8%) had cerebral malaria as defined by the WHO malaria Action programm 1986. fifteen of the 26 patients (57.7%) died – longer duration of unconsciousness before coming to the hospital, hyperparasitaemia, oliguria, recurrent hypoglycemia and convulsions were found to be significantly associated with mortality.[97] In a study done in the South Pacific, the case fatality rate (CFR) in the region was 11.9 % and the prevalence of residual neurological sequelae at discharge was 1.5 %, the proportion of children presenting with deep coma (12%) or hypoglycemia (17%). Clinical or laboratory conditions significantly associated with death were deep coma

such as shock, hypoglycemia and acidosis, should be corrected.[98] Prompt administration of blood transfusions to patients with anemia is likely to reduce the occurrence of death in children with cerebral malaria.[19,75]

The Blantyre coma scale (BCS) provided a better over all assessment of a child's incapacity from *falciparum malaria*, but the Adelaide coma scale (ACS) was more useful in assessing neurological disturbances.[78]

The cause of death and neurological sequelae in African children with cerebral malaria were obscure. Intra-cranial pressure (ICP) was measured and cerebral perfusion pressure (CPP) calculated in 23 Kenyan children with cerebral malaria. Four children had severe intracranial hypertension ICP > 40 mm Hg) : two died, one with an ICP of 158 mm Hg and signs of transtentorial herniation, the other one with an ICP of 42 mm Hg and cardiorespiratory arrest. The other two survived with severe neurological sequelae. Nine had intermediate intracranial hypertension (ICP > 20 mm Hg), all survived without severe sequelae.[100] Mannitol controlled The ICP in children with intermediate hypertension, but it did not prevent the development of severe neurological sequelae.

Intractable intracranial hypertension is a feature of Kenyan children with cerebral malaria and severe intracranial hypertension is associated with a poor outcome. [104]

Eleven cases of cerebral malaria were observed among 106 hospitalized malariarn children. Brief recall of Pathophysiology was given,

including its immunologic aspect, symptomatology and course of this severe form were evoked. All children were treated with intravenous then oral quinine recovered without any neurological sequelae. The importance of a very early treatment was emphasized. A retrospective chart review for the 1993 calendar year, identified 187 children with cerebral malaria admitted to a large teaching hospital in central Ghana, West Africa. The most common clinical presentation were fever, sensorial depression and convulsions in young children experiencing their first episode of malaria.[105] One-half had splenomegaly. Additional features, seen in decreasing frequency, were hepatomegaly, vomiting, abdominal pain and headache. Long term sequelae were identified in 9% and mortality in 6%. Risk factors for central nervous system disease were negative history for previous malaria ($P< 0.005$), and a high percentage of parasitaemia ($P <0.001$). Death or long term sequelae were associated with multiple seizure, and prolonged sensorial depression. The incidence of malaria is currently increasing in Western Africa and young children are more likely than old children to develop severe disease.[101,102] From January to December 1993, 11 cases of cerebral malaria out of a total 106 cases of malaria were admitted in the paediatrics unit of the Yaounde university teaching hospital, these 11 patients were comprised of 6 boys and 5 girls aged 6 months to 10 years with a mean of 4.24 years. Convulsions and coma were the main clinical manifestation in 9 and 11 patients respectively. 10 patients had fever with 1 case of hyperpyrexia, where as splenomegaly

was noted in 6 patients and hepatomegaly in 2. Parasitaemia was between 0.02% and 4%. Chemoprophylaxis was irregular in 2 patients and absent in 9. The average hospital stay was 5.5 days and no death was noted. Twelve cases of an unusual phenomena of ataxia were investigated in otherwise well conscious patients recovering from febrile attack of presumed *falciparum malaria*.[103] The ataxia occurred as the fever was subsiding after febrile period of two to four days . The delay between onset of fever and ataxia was three to four weeks. Peripheral blood of all the patients contained gametocytes of *Plasmodium falciparum*, and in some cases ring stages. The ataxia was most noticeable in the legs, and the clinical picture suggested selective impairment of the cerebeller system. Signs of improvement appeared in a few weeks but complete recovery took one of four months. The most likely pathogenic mechanism of the ataxia in these cases was an immature reaction triggered by the malaria parasite and affecting the cerebellum or its connections, or both.[106]

1.10 Diagnosis of Malaria:

Well-stained thick and thin blood films are needed. The thick one is for the rapid detection of the parasite and the thin is for a more detailed examination in which even species may be identified. The stains used are Giemsa, Field or the leishman stain. The blood film should be repeated at least three times, and it is preferably taken during the febrile period.[107]

A bone marrow examination is sometimes needed when the parasite has not been found in the blood film. It is however performed to exclude malaria.

1.10.1 Malaria pigments.

- Coarse pigments.
- Mural dots in *P. falciparum.*
- Schuffner's dots in *P. vivax.*

Isolation of the gametocytes alone is not enough to confirm the diagnosis of active malaria.

The clinical diagnosis of severe malaria can be difficult for a number of reasons; there are no pathogonomic features in malaria since fever and splenomegaly could be caused by several tropical diseases.[108]

The presence of parasitaemia does not prove that malaria is the cause of a patient's illness, especially in endemic areas where asymptomatic parasitaemia may be common.

Patients with severe malaria are occasionally seen in whom the blood film at the time of presentation, is negative because of previous treatment or a highly synchronous infection. When the disease is suspected, the parasite is looked for in stain-blood smears with Giemsa, Wright – or Field stain. The presence of malaria parasites in the blood may be detected by routine thick

film examination when densities are of the order of 5 to 10 parasite per ul of blood in 100 microscopic fields. [109]

Thick films are more useful than thin films in the detection of a low parasitaemia. Hundred microscopic oil immersions fields on the other hand, and thin blood films are useful in studies of the parasite morphology in erythrocytes and assessment of parasitaemia.

Ring stage and gametocytes are seen in peripheral blood smears in falciparum infection, but not the other mature stages because the mature – parasitized erythrocytes tend to be sequestered in deep tissues. On the other hand all stage of *vivax*, *ovale*, or malaria infections can be seen in peripheral blood smear.[110]

The presence of *P. falciparum* schizonts in peripheral blood is a sign of severity. High parasite densities can be equated with severity, and may wax and wane in the peripheral circulation. Thus it is important to examine serial blood films at intervals of 6 – 12 hours. The presence of malaria pigments in monocytes is a useful indication of the diagnosis of malaria.[111]

Patients with a high clinical suspicion of severe malaria and with repeated negative blood smears for *P. falciparum* could be considered for fine needle aspiration of bone marrow. In such cases aspirates have been shown to contain sequestered parasites diagnostic of severe malaria, as well as presence malaria pigment. Similar results have been reported from intradermal

aspiration. Brace-Chwatt, 1985 used 0.5 ml of a 1:100 solution of adrenaline to stimulate the appearance of parasites in the peripheral blood.[112]

Radio immuno-assay (RIA) method can detect 0.001% parasitaemia. Hybridization probes using genomic or synthetic *P. falciparum* DNA, can detect as a little as 0.001 mg of parasite DNA after one week of exposure. These probes will be invaluable tools for epidemiological studies.

1.10.2 Electroencephalography:

A single EEG data on admission can hardly give enough information for prediction of the clinical coarse and outcome of cerebral malaria. Serial EEGs probably provide more useful information regarding the prognostic signs in this group of patients [114]

Nevertheless, EEG could be useful to rule out some cerebral pathology such as space occupying lesions, epilepsy or any other causes of unconsciousness that could produce similar cerebral symptoms in malaria patients.

1.10.3 Magnetic resonance imaging of the brain:

In patients with cerebral malaria,[115] MRI revealed that brain volume during acute cerebral malaria was slightly greater than that during the convalescent phase of the disease. This difference was attributed to an increase in the volume of intra-cerebral parasites than severe malaria itself. This increased volume probably resulted from sequestration of parasitized erythrocytes and compensatory vasodilatation rather than from oedema. Brain

stem herniation may occur, but its temporal relation to brain death in cases of cerebral malaria remains uncertain.

1.10.4 Other Important Laboratory findings:

In *P. falciparum* infection blood leukocyte count is usually low or normal, but leukocytosis has been found in patients with the most severe disease. Tumour necrosis factor (TNF) concentration may be responsible for leukocytosis. The erythrocyte sedimentation rate is very high. Plasma volume increased to maintain effective circulation of blood volume in the presence of generalized vasodilatation and falling haematocrit.[63]

Hypoglycaemia is a complication of falciparum malaria. It can be due to treatment with quinine, which increases the level of insulin in plasma. Lactic acid levels in both blood and cerebro-spinal fluid (CSF) are high especially with hypoglycemia, as a result of anaerobic glycolysis in both host and parasite and may be lethal. Mean venous blood lactate concentration was found to be almost twice as high in fatal cases as in survivors and correlated with levels of tumor necrosis factor and inter-leukin 1-alpha.[116]

Blood venous glucose concentrations, lower in fatal cases than survivors. Patients who treated with quinine were associated with significantly more episodes of hypoglycemia when compared with artemether or chloroquine.

The platelets count is often reduced from intravascular lysis by immune mechanism and rarely, platelets may be invaded by malaria parasite. Coagulation abnormalities resulting from failure to synthesize clotting factors, and hypo-albuminaemia may occur. Haematocrit or haemoglobin concentration as indication for transfusion should be measured.

Microscopy and culture of CSF is important in patients with cerebral malaria to exclude other treatable encephalopathies. In cerebral malaria the CSF may contain a few lymphocytes and increased protein concentration. The CSF glucose will be low in hypoglycaemic patients and this result may be the first indication of hypoglycemia.(117)

Urine should be examined by microscope and dipstix. Common abnormalities are proteinuria, microscopic haematuria, haemoglobinuria, and red cell casts. The urine is black in patients with severe Intra vascular haemolysis.(51)

1.11 *Plasmodium falciparum* parasitaemia:

Parasitaemia has been used as an index of severity since 1973, when Field and Niven working in Kuala Lumpur and Peninsular Malaya, noted that parasitaemia over 100.000 / cum was correlated with increased mortality, and half of the patients with parasitaemia over 100.000/cum died. Although, some patients appear to tolerate very high parasitaemia with few symptoms, other die with low numbers of parasites in peripheral blood. This phenomenon is explained by studying the distribution of the parasite in the body depending

on the relationship between peripheral parasitaemia and total parasite biomass. Assessment of the sequestered parasitized erthyocytes depends on differential parasite stages development, as shown in peripheral blood film with a predominance of either small, medium or large ring form.

The relationship between parasite size and severity was noted by Field and Shure in 1956, who mentioned that some of the largest number of falciparum trophozoite seen in blood films in Malaya have been associated with severe infection.[13]

Although the study of asexual parasite stages by Jiang et al, 1982, compared the diameter of the nucleus and the cytoplasm of parasite in blood film. This method was used to distinguish fatal cases from non fatal.

Predominant small rings in peripheral blood indicate that the sequestered parasites must be those of the previous cycle while, predominantly large rings indicate that sequestration of the current generation of parasite has begun.[118]

The evaluation of effectiveness and comparison of antimalarial drugs depending on studying their action on developmental stages of the parasite. For example Artemesinine affects ring forms more than mature stages, on the other hand, chloroquine affects principally large ring and young Trophozoite stage.[119]

Obviously, the tiny and small ring parasite stages may present in circulation at the time of peak blood anti-malarial drug concentration.

Thus, the study of parasite developmental stages provides an important prognostic information about distribution of stages in peripheral blood, assessment of sequestered erythrocytes and studying anti-malarial drugs.[120]

1.12 Management of severe Falciparum Malaria In Children:

In the tropical area including the Sudan, malaria is one of the greatest cause of morbidity and mortality in children. Its presentation depends on whether the child is suffering from a recent acute infection, from frequent re-infection, or a continued prolonged infection. The child is dull, restless, has loss of appetite and vomits and there could be severe colicy pain and diarrhoea.[121] Temperature may rise to 38-40 degrees. Fever may be continuous, intermittent or remittent and rigors are uncommon but convulsions and coma can occur. Hepatosplenomegaly with abdominal tenderness can also occur. Anaemia with a Hb level of 5 mg/dl or less can be a presenting feature. [29]

Children with falciparum malaria can deteriorate rapidly with increase in parasitaemia and development of severe manifestation like severe anaemia. They should be managed as a medical emergency.

1.12.1 History:

In the history it is interesting to ask about fever and its pattern, abdominal pain, diarrhoea. History of infection with malaria before, convulsions and history of residence or travel should be sought since multi – drug resistance occurs in certain regions of world.

1.12.2 Physical examination:

A brief initial physical examination should be carried out to assess hydration and detect pulmonary oedema and other severe manifestation or complication which would require immediate treatment. Thick and thin blood film and measurements of haematocrit must be done. In children with altered consciousness or convulsions, blood glucose and Lumbar puncture must be done.[87] If parasitological confirmation is likely to take more than one hour, treatment should be started in sick patients before confirmation of the diagnosis. Immediate therapeutic measures are correction of hypoglycaemia, treatment of convulsions, lowering an excessively high temperature, and setting up an intravenous infusion for fluids and antimalarial therapy. In severely anaemic children blood transfusion may be urgently required. Antimalarial should be given if possible by intravenous infusion.[105] Oral administration of the drug should replace parental therapy as soon as possible. Children should be weighed and the doses of antimalarial should be calculated on a mg/kg basis (Chloroquine should be given). Fluid requirement must be assessed in each individual case and to set up intravenous infusions so that the appropriate quantity fluid and antimalarial drug are delivered.[25] Unconscious children should receive regular glucose to prevent starvation hypoglycemia .

Convulsions are common in children, either with cerebral malaria or malarial associated convulsions, and they are considerably associated with

mortality and sequelae, so they must be treated immediately with intravenous diazepam or paraldehyde. If circumstances do not permit intravenous infusion, chloroquine and quinine may be given by Intra muscular injection. The majority of those who recover from cerebral regain consciousness within thirty-six hours. Quinine at this stage can be given orally by a nasogastric tube.[86]

If the haematocrit is below 20%, blood transfusion must be given after screening of the blood and assessing the general condition of the patient (e.g. shock and heart failure).

Hypoglycemia should be managed by 50% or 10% glucose. Blood glucose must be checked frequently.[88]

Since there is no parentral antipyretic for children paracetamol suppositories can be used in addition to simple maneuvers like tepid sponging or fanning to keep the rectal temperature below 39^0C. Nausea and vomiting usually subside after the fever has been controlled.[49]

1.13. Chemotherapy of Malaria:

Severe malaria is a medical emergency requiring immediate administration of rapidly effective antimalarial drugs. Parenteral treatment is needed in the acute stage, but as soon as the patient is able to take fluid by mouth oral treatment should be substituted. If it is not possible to give parenteral treatment, then treatment by mouth or via nasogastric tube should be started immediately as drug absorption appears to be adequate even in

severe malaria. There is still much to be learned about the rapidity of parasite clearance and stage specificity of antimalarial drugs. [110]

1.13.1 Chloroquine:

Chloroquine is a 4-aminoquinoline compound. It is a potent antimalarial drug in strains that are not resistant, and highly effective against the asexual erythocytic form of all four species of malaria. The mechanism of action on plasmodia has not been fully elucidated. It has been suggested that it acts through an interaction with DNA and DNA-RNA polymers. Chloroquine is rapidly absorbed after oral administration in adults and children, and usually absorption is complete even in very severe infections. It found in blood constituents such as thrombocytes and granulocytes. The time for peak concentration in severe malaria is usually 20 minutes and can be as short as 5 minutes.

Chloroquine concentration in red blood cells is approximately three times higher than plasma and is eliminated slowly from the body and may persist for a long period. Chloroquine is formulated as phosphate, hydrochloride or sulphate salt. The usual treatment dose is 25 mg salt/kg for adult, 5 mg salt/kg for children.[105,122]

1.13.2 Amodiaquine:

Amodiaquine is at least as effective as chloroquine against chloroquine– sensitive *P. falciparum*. Parasites with resistance to chloroquine may remain sensitive or be less resistant to Amodiaquine.[123]

The main concern is that Amodiaquine causes a high incidence of agranulocytosis and hepatitis.[124,125]

1.13.3 Quinine:

Quinine is the treatment of choice for chloroquine – resistant malaria. Quinine sulphate is well absorbed when given by mouth to healthy subjects and those with uncomplicated malaria. The peak plasma concentrations of quinine are reached in one to three hours, but should not be given subcutanously because this can result in skin necrosis. [117]

Quinine is distributed in most of the body fluids, but the mean concentration is in red cells, and is approximately one- third of that in plasma, rising to one half (presumably because of concentration within malaria parasites). In severe malaria the terminal elimination half – life in healthy adult subjects is 11 hours, compared with 16 hours in uncomplicated malaria and 18 hours in cerebral malaria, but elimination is more rapid in children and pregnant women.[126]

The dosage is assessed by weighting of salt, thus the maintenance dose of quinine is 17 mg salt / kg for adult, and 10 mg salt / kg for children. Ototoxicity induced by quinine is almost completely reversible.[117,127]

1.13.4 Mefloquine:

Mefloquine is a quindinemethanol compound, which structurally resembles quinine. It is effective against all malaria species including multi-drug resistant *P.*

falciparum with treatment dose 15 mg/kg. Plasma or whole blood concentration exceeding 500 mg /ml are usually reached within 6 hours.

Elimination half- life is approximately three weeks. Halofantrine and pyronaridine, like Mefloquine, are effective against multi-drug resistant falciparum malaria.[128]

1.13.5 Sulphadozine- pyrmethamine:

This is the most widely used of a family of drug combination, which antagonizes parasite folic acid synthesis. They are both well absorbed with peak plasma concentration reached in 2 to 6 hours. Red cell concentrations of both drugs are less than half those in plasma. The terminal elimination half-life is approximately 90 hours.[129]

1.13.6 Alpha, Beta, Artemether:

Is an ethyl ether derivative of artemisinin which is an efficient schizontocidal drug in mild to complicated falciparum malaria. It is given intramuscularly 150 mg once daily on 3 consecutive days. The median fever clearance time is 72 hrs. range (12-120 hrs.) and the median parasite clearance time is 2 days (range 1-4 d). Rapid recovery from coma was observed in cerebral malaria patients (after a median of 18 h, range 6-72 hours).[130,131]

JUSTIFICATION

- Malaria of *P. falciparum* is considered the most frequent cause of morbidity and mortality in children in endemic areas like Sudan.
- The most important complications of *P. falciparum* infection in children are cerebral malaria, repeated convulsions, severe anaemia and neurological deficits. The majority being preventable.
- No study dealing with neurological manifestations of *P. falciparum* has been conducted in Sudan before.

OBJECTIVES

1. To detect the pattern of neurological manifestations of falciparum malaria in

   children above 6 years of age.

2. To evaluate the role of the following risk factors in relation to neurological presentation, severity and outcome of falciparum malaria in these children.

   - Level of parasitaemia.
   - Level of consciousness.
   - Absent corneal reflex.
   - Hypoglycemia.

2. PATIENTS AND METHODS

2.1 PATIENTS:

2.1.1 Nature of the study:

It is a prospective hospital based study carried during the period from November 1996 to November 1997 in Khartoum Children Emergency Hospital (KCEH).

2.1.2 Place of the study:

Khartoum Children Emergency Hospital (KCEH) is the largest referral paediatric emergency hospital The total number of patients presented to the Outpatient Department (OPD) were 14108, monthly of whom 9.475% were admitted, and those who attended the follow up Referred clinics were 2939. The mortality rate was 4.7%in 1995(with malnutrition, gastroenteritis, ARI, and septicemia topping the list). KCEH consists of 99 beds, different wards for emergency admissions including a general ward, ward for acute respiratory infection, diarrhoeal disease, isolation unit with 23 beds, nutritional unit, vaccination content, and follow up referred clinics conducted by pediatricians and paediatrics registrars.

The catchment area includes Khartoum City and its extensions around a diameter of 30 km, with an estimated population of 3.875.344 in 1995 mostly urban. It also serves the unplanned settlements in the area of Khartoum mostly inhabited by displaced population from west & south. It has

a good statistical department. Children with acute illness are admitted for 24-84 hours, for emergency management and urgent investigations; those who improved were discharged and those who required further investigations and management were referred to the specific paediatrics wards

2.1.3 Duration of the study:

The study was conducted during the period between November 1996 to November 1997.

2.1.4 The study group and sampling techniques:

Two hundred patients above 6 years of age seen at Khartoum Children Emergency Hospital with a positive blood film for falciparum malaria.

2.1.5 Sample size

One hundred children above 6 years of age with confirmed positive blood film for falciparum malaria, who presented with acute neurological symptoms and signs were included in the study.

Another 100 children above 6 years of age who had positive blood film for falciparum malaria without neurological manifestations were also included as a control group.

2.2. METHODS

2.2.1 Technique:

A questionnaire was designed in which informations obtained from each child were entered. The response to treatment and progress were monitored.

Follow up of the patients was done in the ward, at the referred clinic and after 2 months of discharge.

2.2.2 Questionnaire:

Every child included in this study was admitted to one of the paediatrics wards at Khartoum Teaching Hospital. A thorough and comprehensive history was taken and detailed examination was performed on each child. Data obtained was entered in a designed questionnaire sheet. Other data were obtained such as lab tests, associated diseases, treatment regimen clinical progress of the individual patient & follow up observation.

2.2.3 History:

Included a complete and detailed history with a special emphasis on the duration of fever, convulsions, and loss of consciousness.

2.2.4 Examination:

Detailed examination with special emphasis on anaemia, hepatosplenomegaly, degree of coma, presence of decortication,

decerebration, corneal reflex, dilated pupils, weakness, or hypertonicity and cranial nerve palsies.

Level of consciousness was evaluated according to modified Glasgow coma scale for children. For practical purposes coma was further divided whereby deep coma [unarousable coma] = (up to 7), light coma = (8-14) and full conscious [15 and above] to aid in analysis. Liver and spleen enlargement were measured below the costal margin at the nipple line and recorded in cm. All children with disturbed consciousness had L. P. done to exclude meningitis or encephalitis after fundoscopy.

2.2.5 Investigations:

Were conducted by the senior technician at C 15 laboratory

- Blood film for malaria (Thick & Thin).
- Degree of parasitaemia.
- Blood sugar level.
- Hb% PCV.
- TWBC.
- CSF for protein cells and sugar.
- Urine general .

2.2.6 Blood sample collection:

While the patient is sitting, the cubital fossa was swabbed with a sterile cotton piece soaked in 95% alcohol. The cubital vein was selected and 5 ml

of whole blood drawn using a disposable syringe. Immediately, thin and thick blood films were done for malaria parasite. One ml of blood was collected in a tube containing EDTA anticoagulant for hemoglobin and PCV estimation and random blood sugar.

The samples and the sheet were given the same serial number. The collected blood samples, were tested within 4 hours for hemoglobin, PCV and blood film for malaria and the degree of parasitaemia.

Malaria parasitaemia was quantified according to a standardized scale, whereby + 1 represents 1-10 malaria parasites/100 high power field (HPF ×1000) i.e. light parasitaemia and + 4 refers to more than 10 parasites/HPF (i.e. heavy parasitaemia) 1 parasite / HPF = 500 parasites/UL.

The blood film for malaria and degree of parasitaemia were examined using Giemsa stain. Severe anaemia defined as a haematocrit of 20.0% or less. Hypoglycemia as blood glucose of 2.2 mmol/dl or less (40mg/dl or less).

All the above investigations were done in patients with acute neurological manifestations and in the control group as well, except the CSF examination since it is not ethical to obtain CSF sample in patients without neurological symptoms and signs.

2.2.7 Management:

Oxygen, Diazepam, antimalarial were administered. Chloroquine was administered according to the therapeutic dose to patients who have no

neurological manifestations and quinine to those with neurological manifestations.

Response to treatment was followed up by improvement of the general condition, fall of temperature, and recovery from loss of consciousness.

2.2.8 Inclusion Criteria:

Any child above 6 years of age with a positive blood film for falciparum malaria.

2.2.9 Exclusion Criteria:

Children who were known to have epilepsy and previous neurological handicap.

Children who had encephalitis or meningitis confirmed by CSF examination.

2.2.10 Statistical analysis:

The results of the different variables and the laboratory Results were analyzed, using Statistical Package for Social Sciences (SPSS), simple frequency and Chi square test were used. 0.05 probability level was used for significant testing.

3. RESULTS

3.1 Case identification:

Hundred Patients with neurological manifestations of P.F malaria were studied in the period between November 1996 to November 1997.

The clinical and parasitological diagnosis of plasmodium falciparum malaria was made. All children were above 6 years of age. One hundred of them had neurological manifestations of P.F. malaria (study group) and another one hundred had positive blood film for malaria but without neurological manifestations (control group). Males constituted the majority of patients 57 (57%) presented with either neurological or non-neurological manifestations (**Table 1**).

Most of the patients were in the age group from above 6-12 years constituted 73(73%) with neurological manifestations and 81(81%) without neurological manifestations (**Table 2**). There was no significant difference between the two groups regarding the age and the sex.

3.2 Symptoms:

None of the patients whether with neurological manifestations or without neurological manifestations presented before 24 hours of their illness.

Table 1: Sex Distribution in-patients with and without neurological manifestation of PF malaria

Sex	**Study Group** No **(%)**	**Control Group** No **(%)**
Male	57 **(57)**	63 **(63)**
Female	43 **(43)**	37 **(37)**
Total	100 **(100)**	100 **(100)**

$P < 0.04$

Table 2: Age Distribution in-patients with and without neurological manifestation of PF malaria

Age (in years)	**Study Group** No **(%)**	**Control Group** No **(%)**
> 6 – 9	47 **(47)**	47 **(47)**
10 – 12	27 **(27)**	34 **(34)**
13 – 15	26 **(26)**	19 **(19)**
Total	100 **(100)**	**100 (100)**

P < 0.02

Ninety–seven (97%) patients in study group with neurological manifestations and 89 (89%) patients without neurological manifestation presented within 1 –7 days, and 3 (3%) patients with neurological manifestation and 11 (11%) patients without neurological manifestation presented after 7 days duration of illness (**Table 3**).

Fever and headache were the main presenting symptoms in patients with or without neurological manifestation this constituted 85 (85%) and 75 (75%) in the first group, and 90 (90%) and 68 (68%) in the second group respectively. Vomiting, on the other hand, was encountered more in patients without neurological manifestations in (**Fig. 1**). The main neurological symptoms were convulsions in 32 (32%) patients, loss of consciousness in 63 (63%) patients, and in drowsiness 48 (48%) patients.

The percentage of deaths within the study group and the control group was 10% and 1% respectively (**Table 4**). Number of deaths was significantly different between the two groups with the P value less than 0.05.

Table 3: Neurological signs of malaria in relation to the duration of illness

Duration in Days	**Study group** No	**(%)**	Control group No	**(%)**
< 1 day	0	**(0)**	0	**(0)**
1-3	90	**(90)**	82	**(82)**
4-7	09	**(09)**	07	**(07)**
> 7	01	**(01)**	11	**(11)**
Total	100	**(100)**	100	**(100)**

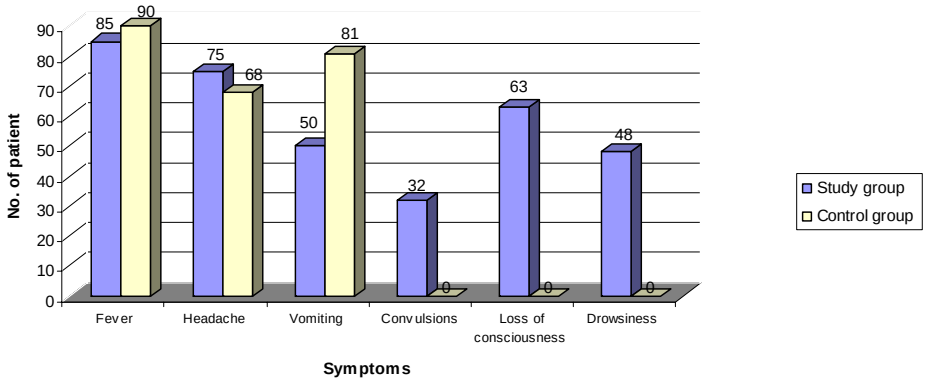
P < 0.02

Table 4: Neurological manifestations in malaria and the outcome in patients of the study

Outcome	**Study group** No **(%)**	Control group No **(%)**
Survivals	90 **(90)**	99 **(99)**
Deaths	10 **(10)**	01 **(1)**
Total	100 **(100)**	100 **(100)**

$P < 0.001$

Fig. 1: Distribution of different symptoms of Plasmodium falciparum malaria



Out of 32 patients who presented with convulsions due to P.F. malaria, 20 (62.5%) had generalized convulsions and 12 (37.5%)

presented with focal ones. Duration of the attacks was found to be < 15 Minutes in 17 (53%) patients and > 15 minutes in. 15 (47%). In 8 (25%) patients convulsions were found to be single and in 24 (75%) they were multiple.

3.3 Past History:

Three (3.0%) patients in the study group of P.F malaria, and 1 (1%) patients in the control group had a past history of cerebral malaria. Twenty (20%) patients with neurological manifestations and 8 (8%) patients without neurological manifestations had a past history of chloroquine resistant malaria. Past history of recent malaria [within two weeks] was found in 34 (34%) patients with neurological manifestations of *P.F* malaria. There were no reported quinine or fansidar resistant malaria cases.

3.4 Family and drug History:

Ten patients in the study group and 4 (4%) patients in the control group had a positive family history of febrile convulsions.

Positive family history of epilepsy was found in only one patient of the study group.

Chloroquine was the only antimalarial drug taken by the patients in the previous two weeks, before their presentation (**Table 5**).

Table 5: Distribution of antimalarial drugs in study and control group

Drug	Study group		Control group	
	No	(%)	**No**	(%)
Chloroquine	37	**(37)**	25	**(25)**
Fansidar	5	**(5)**	3	**(3)**
Quinine	5	**(5)**	1	**(1)**

3.5 Physical examination:

Eighty-five (85%) patients in the study group and 80 (80%) patients in the control group were found to be febrile [>37c^{o}] in the study group & the control group 43(43%) & 31(31%) patients were found to be anemic [< 10 gm/dl] respectively. Whereas dehydration was found in 7 (7%) patients with neurological manifestations and 11 (11%) patients without neurological manifestations.

Regarding the fever, anaemia and dehydration there were no significant statistical difference between the two groups.

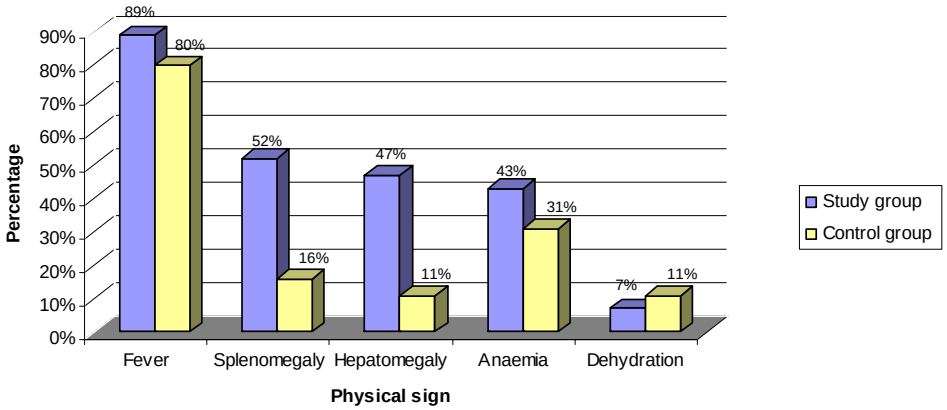
Splenomegaly was found in 52 (52%) patients in the study group and only 16 (16%) patients in the control group.

As well patients with hepatomegaly in the control and study group respectively was found in 47 (47%) patients and in only 11(11%) patients in the study & control group respectively (**Table 6** and **Fig. 2**).

Table 6: Distribution of physical findings in patients of the study and control group.

Physical finding	Study group **No** (%)	Control group No (%)
Fever	89 **(89%)**	80 **(80%)**
Splenomegaly	52 **(52%)**	16 **(16%)**
Hepatomegaly	47 **(47%)**	11 **(11%)**
Anaemia	43 **(43%)**	31 **(31%)**
Dehydration	07 **(07%)**	11 **(11%)**

Fig. 2: Distribution of physical findings in patients with and without neurological manifestations of P. F. malaria



3.6 Central Nervous System Examination:

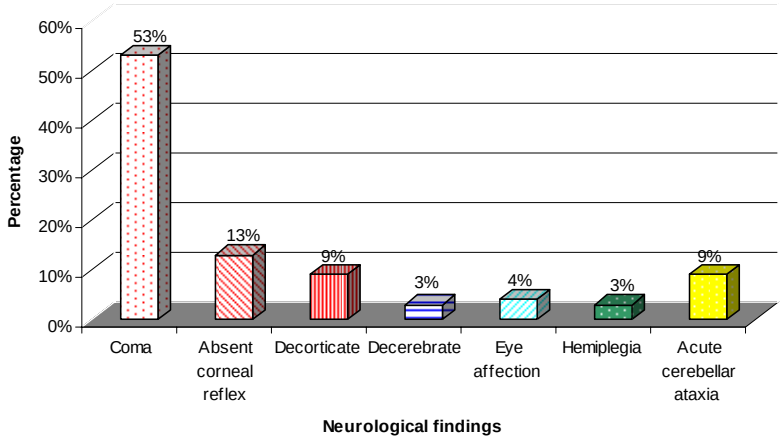
As mentioned previously there were no neurological manifestations in the control group.

On examination of the study group the neurological manifestations were as follow: light coma in 22 (22%), deep coma in 31 (31%) (Glasgow coma scale), decorticate posture in 5 (5%), decerebrate in 3 (3%), right 6th nerve palsy in 2 (2%), cortical blindness in 4 (4%), deconjugate gaze palsy & right sided squint in 2 (2%), absent corneal reflex in 30 (30%), right sided hemiplegia in 2 (2%) and acute cerebeller ataxia in 9 (9%) (**Table 7, Fig. 3**).

Table 7: Distribution of Neurological findings in patients with neurological manifestations of *P. F. malaria*

Neurological findings	Neurological Cases No **(%)**
Light coma	22 **(22)**
Deep coma	31 **(31)**
Absent Corneal reflex	13 **(13)**
Decorticate posture	05 **(05)**
Decerebrate posture	03 **(03)**
Eye affection	04 **(04)**
Hemiplegia	03 **(03)**
Acute cerebeller ataxia	09 **(09)**
Total	90 **(90)**

Fig. 3: Distribution of neurological findings in study group



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Multiple convulsions which was one of the risk factors and was reported in all patients. It was seen in 2(100%) presented with aphasia, 4(80%) of patients presented with decorticate posture, and in 70% of patients who died of P.F. malaria, while it was reported less frequently with the other neurological manifestations (**Table 8**).

Absent corneal reflex was reported in all patients [3] presenting with decerebrate posture and was not found in-patients presenting with convulsions or aphasia. It was however commonly found in 80% [2] & 70% [7] of patients presenting with decorticate posture and those who died respectively (**Table 9**, **Fig. 4**).

Deep coma which was considered as the third risk factor was reported in all patients of decorticate posture 5(100%), in 3(75%) patients with eye affection (**Table 10, Fig. 5**).

3.7 Investigations:

Packed cell volume (PCV) < 20 was found in 43 (43%) patients with neurological manifestations and in 31(31%) patients without neurological manifestations (**Table 11**).

Regarding the severity of anaemia there was significant statistical difference between the two groups $P < 0.05$.

Table 8: Neurological Manifestation in relation to Multiple convulsions

Neurological Manifestation	Number of patients	Multiple convulsions	**(%)**
Loss of Consciousness	53	24	**(87)**
Hallucination	23	09	**(39)**
Cerebellar ataxia	09	06	**(66)**
Aphasia	02	02	**(100)**
Eye affection	04	02	**(50)**
Hemiplegia	03	02	**(66)**
Decerebrate posture	03	01	**(33)**
Decorticate posture	05	04	**(80)**
Death	10	07	**(70)**

Table 9: Neurological Manifestation of *P. F malaria* in relation to Absent Corneal Reflex

Neurological Manifestation	Number of patients	Absent Corneal reflex	**(%)**
Convulsions	32	0	**(0)**
Loss of Consciousness	53	13	**(45)**
Hallucination	23	02	**(08)**
Cerebellar ataxia	09	02	**(22)**
Aphasia	02	00	**(0)**
Eye affection	04	02	**(50)**
Hemiplegia	03	01	**(33)**
Decerebrate posture	03	03	**(100)**
Decorticate posture	05	04	**(80)**
Death	10	07	**(70)**

Fig. 4: Neurological manifestations of Plasmodium falciparum malaria in relation to absent of corneal reflex

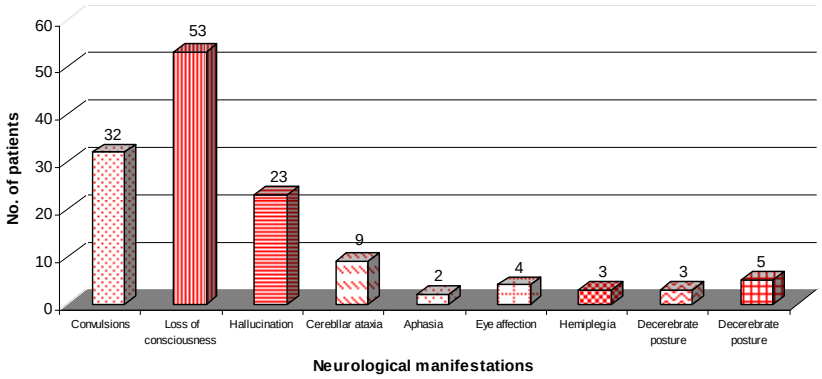

Table 10: Neurological Manifestation of P. F malaria

in relation to Deep coma

Neurological Manifestation	Number of patients	Deep coma	**(%)**
Convulsions	32	0	**0**
Absent Corneal reflex	53	10	**18.8**
Hallucination	23	1	**4.34**
Cerebellar ataxia	9	5	**55.6**
Aphasia	2	1	**50**
Eye affection	4	3	**75**
Hemiplegia	3	2	**66.6**
Decerebrate posture	3	2	**66.6**
Decorticate posture	5	5	**100**
Death	10	6	**60**

Fig. 5: Neurological manifestations in relation to deep coma

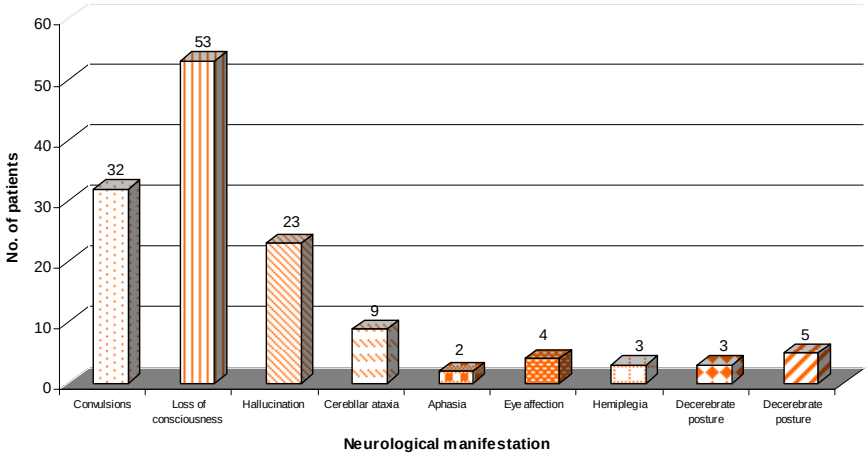

Table 11: Distribution of PCV in patients with & without neurological manifestations of *P.F. malaria*

PCV	**Study group** No **(%)**	**Control Group** No **(%)**
> 20	57 **(57%)**	69 **(69%)**
< 20	43 **(43%)**	31 **(31%)**
Total	100 **(100%)**	100 **(100%)**

P< 0.04

Heavy parasitaemia, the fourth risk factor, was found in 42(42%) patient in the study group in comparison to 24 (24%) patients in the control group (**Table 12**).

The fifth risk factors, hypoglycemia (< 40 mg/dl), was found in 24 (24%) patients in the study group and in only 3 (3%) patients in the control group.

The rest of patients were normoglycemic (>40 mg/dl) (**Table 13**).
The difference was statistically significant ($p < 0.05$).

3.8 Follow – up:

The follow up was done in the ward, on discharge, after one month, and after two month. Eighty-nine (89%) patients with neurological manifestations showed improvement in the level of consciousness 1 (1%) patient was static and 10(10%) became worse. Temperature dropped in 97 (97%) patients without neurological manifestations and in 93(93%) patients with neurological manifestations i.e. fever did not affect the result.

Residual disabilities (e.g. Hemiplegia-aphasia) were reported in 18 (18%) patients with neurological manifestations on discharge. However after one month they were still present in 10 patients, and after 2 month in only 7 patients.

Table 12: Distribution of level of parasitaemia in patients with and without neurological manifestation of P.F malaria

Level of Parasitaemia	**Study group** No **(%)**	**Control Group** No **(%)**
Light parasitaemia	58 **(58%)**	76 **(76%)**
Heavy parasitaemia	42 **(42%)**	24 **(24%)**
Total	100 **(100%)**	100 **(100%)**

P<0.03

Table 13: Distribution of Random Blood Sugar (RBS) in patients with and without Neurological Manifestation of *P.F malaria*

RBS (mg/dl)	**Study group** No **(%)**	**Control Group** No **(%)**
> 40	76 **(76)**	97 **(97)**
< 40	24 **(24)**	3 **(3)**
Total	100 **(100%)**	100 **(100%)**

P<0.04

4. DISCUSSION

4.1 General characteristics of the patients:

The results of the study showed that males were affected more commonly than females in both the study and control group, 57% and 63% respectively .The main age groups affected were > 6-9 & 10- 12 years constituted more than 70% in both groups. More than 50% of patients in both groups presented in the first three days of their illness .In a study done by Hashim in 100 Sudanese children with cerebral malaria the same results regarding the age, sex and duration of presentation were found.[122]

In this study males outnumbered females. This finding could be attributed to the increase in the number of males in the study area. Because of the presence of the study area in a mesoendemic to holo -endemic zone where transmission is unstable, falciparum malaria affects all age groups. However, in this area the disease strikes children less than five years old more commonly. In the areas of stable intense malaria transmission the incidence and density of malaria parasitaemia decline with age, a phenomenon that has long been interpreted as being the result of antimalarial immunity.[67]

4.2 Symptom of P.F. Malaria:

The most frequent symptom was fever in 85(85%) in neurological cases and 90 (90%) in non-neurological case. In a study in New Guinea a lower percentage of patients 56% was reported to present with fever.

However, a comparable percentage of patients was recorded in Tanzania. These children who presented to hospital with no fever may be either due to having received treatment at home or probably brought to clinic in the non-febrile phase of an intermittent fever. Genton in a study to correlate between the fever and the degree of parasitaemia showed that a positive correlation does exist.[111]

Vomiting, one of the abdominal manifestations attributed to malaria was recorded in 47(47%) in neurological cases and in 67(67%) of non-neurological cases. The difference between the two groups was significant ($P < 0.05$). This higher frequency was more than reported in the other studies done in Tanzania and New Guinea in which the incidence of vomiting was 15% in Tanzania and 17% New Guinea [117]. Headache was found in most of the patients in the two groups (75%) and (68%) respectively. Since our patients in this study were above 6 years of age, they were able to describe headache very well compared to those of Tanzanian where the age of the study group was from 1 to 15 years.[27]

4.3 Past history:

Past history of cerebral malaria seems not to be important, whereas past history of chloroquine resistant malaria and past history of recent malaria were probably an important factors, and this may be due to immunological factors.

4.4. Family and drug history:

Positive family history of febrile convulsions was more in the study group, and this may precipitate the neurological manifestations. Chloroquine was the only antimalarial drug taken by the patients in the previous two weeks, in spite of these the patients presented with complications, and this may due to poopr efficacy of the drugs or its improper use.

4.5 Physical Signs of P.F Malaria:

Thirty two (32%) out of 100 patients with neurological manifestations of *P.F* malaria were found to have convulsions, 20 (63%) of them presented with generalized convulsions and 12(38%) patients presented with focal convulsions. This is in contrast to higher percentage of patients recorded from Kenya where partial motor seizures were more than generalized ones.[57] The explanation of the differences in these two studies may be attributed to some genetic variations of the parasite or the host. The frequency of convulsions in neurologically complicated cases is consistent with the observation reported by Sailssy who found that two third of children with cerebral malaria had convulsions.[20]Molyneux noticed that convulsions may herald cerebral malaria in up to 82% of children.[77]Wattanagoon concluded that convulsions are important complications of malaria in children and are specifically with P.F infection even in other wise uncomplicated malaria.[94] In a study done by Akpede, convulsion with malaria are more often a manifestation of cerebral

dysfunction rather than being simple febrile in nature [100]. All forms of cerebral dysfunction in malaria including repeated convulsions should be managed as being clinical manifestations of cerebral malaria.

Other important symptoms like hallucination, loss of consciousness, drowsiness, unsteadiness and weakness were present in patients with neurological manifestations of *P.F* malaria. Most of the patients in the study group and in the control group showed positive history of recent malaria and drug history of chloroquine ingestion. In a study done by Hashim one third of the patients had a positive history of malaria.[122]This can be explained by the fact that malaria parasites exhibit considerable variation diversity and they readily undergo antigenic variation. Therefore the importance of the immune system in controlling and eradicating parasite can hardly be depended on. Splenomegaly and hepatomegaly were found in about 50% of patients with neurological manifestation of *P.F* malaria and this high in comparison to other studies, indicating that visceral enlargement is common in the Sudan.[25]Molyneux reported hepatomegaly in two third of children with cerebral malaria and splenomegaly in one fourth of them.[77] Mabeza detected splenomegaly in half of the children with cerebral malaria and hepatomegaly in one third of them.[92] Hepatomegaly was observed in half of children with cerebral malaria.[45] The spleen seems to play a central role in the clearance of parasitized erythrocytes. The spleen is able to recognize the loss of deformability of parasitized erythrocytes and plays a role in opsonization

with antibodies and complements. In acute falciparum malaria, removal of infected erythrocytes was increased in patients with splenomegaly. [31]

4.4 Neurological Signs and sequelae of *P.F* malaria:

Deep coma occurred in (31%) patients with neurological manifestations, while in 115 Gambian children 46% has deep coma[95]. Molynenx reported that depth of coma in cerebral malaria was correlated with mortality and neurological sequelae. Gambian children with cerebral malaria, deep coma was associated with mortality of 31% compared with 10% in moderate coma. In this study decorticate and decerebrate posture, hemiparesis, cranial nerves and acute cerebeller ataxia were reported, the same findings were reported in children with cerebral malaria from elsewhere[78,81,83]

Fundal examination of all patients enrolled in this study was normal. Papilla-oedema and retinal hemorrhage were reported to predict poor outcome in cerebral malaria. [105] About 9-12% of patients in the study group had neurological disabilities in the form of acute cerebeller ataxia, Hemiplegia, six nerve palsy, cortical blindness and aphasia. This is in comparison to a study done in Kenya where 50% of the 58 children with cerebral malaria presented with attenuated forms of sequelae[57]. Cortical blindness had regressed completely, unlike ataxia and loss of balance. Acute cerebeller ataxia, which occurred in 9 patients in this study and grading between mild to moderate, when compared to a study done in Sudanese adult,

was found to be less frequent and less severe[106]. The correlation between repeated seizures and other neurological manifestations was consistent with the observation.

Jaffar reported that more than 96% of Ghambian children who died of falciparum malaria had repeated convulsion.[105] More over convulsions may herald deep coma in up to 82% of children[78]. Crawley reported that prolonged multiple seizures may play an important part in the pathogenesis of coma in cerebral malaria, and were associated with development of neurological sequelae.[86] One third of patients with deep coma and 70% of deaths had absent corneal reflex, which also occurred with other neurological manifestation and sequelae it can be an important factor in prognosis and outcome of plasmodium falciparum malaria.[83] Deep coma occurred in > 50% of patients with cerebeller ataxia, 50% of patients with aphasia, in most of patients with eye affection, in two –third of patients with Hemiplegia and in most cases with decerebrate and decorticate postures [89]. Deep coma as well was reported in 6 deaths out of 10, so it was an important factor in morbidity and mortality of falciparum malaria, in this study.[95] The same finding was reported by Marsh in a study done in Kenya, he concluded that in African children with P.F. malaria, one of the predictors of a fatal outcome following childhood cerebral malaria was deep coma. [89]

4.5 Investigations:

Severe anaemia (PCV<20) was in 43(43%) patients with neurological manifestations and in 31(31%) patients without neurological manifestations.[110] The incidence was high in both groups. Although malaria is unstable in this study area, the incidence of anaemia can be attributed to additional factors such as malnutrition. In areas of stable transmission, anaemia becomes more common than cerebral malaria. Stutsker reported 54% of cases with severe anaemia due to malaria in areas of stable transmission, while the frequents chapped only 32% in areas with unstable malaria among malarian children.[131] In his study heavy parasitaemia was associated with neurological manifestations of malaria more than the non- neurological malaria (P< 0.05), yet there were a lot of patients with light parasitaemia and had repeated convulsions and coma. The same finding was observed by Akpede who reported significant relationship between the severity of parasitaemia and convulsions.[100] Hypoglycaemia occurred in 24(24%) patients with neurological manifestation & in 3(3%) patients with non-neurological manifestation (P< 0.05) Approximately the same finding was found in Gambia and Malawi were 26-32% of children with severe malaria were hypoglycaemic.[80,87,98] Hypoglycaemia occurred in 5 patients with convulsions, in 5 patients with light coma but in 13 patients with deep coma. It was found in 50% of patients with cerebellar ataxia, in 10% of patients with Hemiplegia and in most patients with decorticate and decerebrate postures.[82]Hypoglycaemia was found in 7 out of 10 in the deaths occurred in

patients with neurological manifestations of P.F malaria. It was one of the important factors in mortality and morbidity related to infection of P.F malaria[92].

CONCLUSION

- Neurological manifestations of plasmodium malaria are fairly common and are associated with high morbidity.
- Deep coma, repeated convulsions and hallucinations were the commonest neurological manifestation of P.F Malaria. Acute cerebeller ataxia occurred less frequently. Aphasia and cranial nerve palsies were rare neurological manifestations of P.F Malaria.
- Hypoglycaemia, absent corneal reflexes, deep coma and repeated convulsions were the commonest predictors of neurological sequelae of P.F Malaria.
- Hyperparasitaemia tend to be associated with the neurological cases although there were

hyperparasitaemic patients with mild illness and some neurological cases occurred with light parasitaemia.

RECOMMENDATIONS

On the basis of this study, the following can be recommended as preventive measures against the neurological manifestations of PF malaria.

1. The promotion of malaria control by strengthening the existing national program. Environmental intervention should be involved in the implementation.
2. To increase the awareness of health personnel towards the diagnosis and management of any severe form of malaria including deep coma and repeated convulsions. This could be achieved by introducing a comprehensive course in malaria, in the curriculum of medical school, and medical assistant schools.
3. Early diagnosis as well as proper management of PF Malaria.
4. Repeated convulsions, the most important risk factor for neurological manifestations and mortality should be managed as indicative of cerebral involvement rather than simple febrile convulsions.
5. Careful physical examination should be done in all patients with neurological manifestation *P. F. malaria* to detect any neurological sequelae.
6. Random blood sugar should be obtained to look for hypoglycaemia in every child with neurological manifestations of *P.F malaria*.
7. Further research should be done on the outcome of the neurological sequelae of P.F malaria.

REFERENCES

1. Desjardin RE, Doberstyn EB. lntroducion of malaria. In: Wernsdofer WH, Mcgregar MC (editors) Malaria textbook of principle and practice of malariology, 1st ed. London: Churchill and Livingstone; 1988.
2. Whit e NJ, Warrel DA . History of malaria. In: Wernsdofer W H and Gregar M C (editors) Textbook of Malaria. Edinburgh: Churchill Livingstone; (in press) 1986., 302-37.
3. James J, plorede MO, Nicholas J. Malaria. In: Braunwad E , lsselbac K J . petersdorf RG (editors) Hill book, 11th edition, London: Company; 1987. P. 778-84.
4. Shute PG. The microscopic diagnosis of human malaria, part 11 A morphological study of the erythrocytic parasites. Kuala Lumpur Government Press,1965 .
5. Bradleg DT, Newbold Warrell DA. Malaria. In: Principles Gorrham. London: Black-well Scientific publications; 1966. 5474-502.
6. WHO, World Malaria Situation in 1992, Wkly Epid Rec 1994; 4294: 310-312.
7. Federal Ministry of Health. Annual Report- National Malaria Administration , Sudan 1995.
8. Ministry of Health – Sudan – Annual Statistical Report, 1980 Khartoum.

9. Federal Ministry of Health. Annual Report- National Malaria Administration , Sudan 1998.

10. Marsh K, Greenwood BM. In clinics in Tropical Medicine and Communicable disease 1986; 1:91-125.

11. Boonpucknavig V, Boonpuckanvig S, Udomsangpetch R, Niganent P. An immunofluorescent study of cerebral malaria. Archives of pathology and laboratory Medicine 1990; 114: 1028 – 34.

12. Cally R. Detection of very low level *Plasmodium falciparum* infections using polymerize chain reaction and reassessment of the Epidemiology of unstable malaria in Sudan. Am J Trop Med Hyg 1996; 54:1-5.

13. Field JW, Sandosham AA, Fong YL. The microscopic diagnosis of human malaria I – A morphological study of the erythocytic parasites in thick blood film studies of the Institute for Medical Research Federation of Malaya 1963; 30: 417- 29.

14. Bruce-Chwatt LJ. Essential malariology, 2nd edition. London: William Heinemann; 1985. P. 110.

15. Weatherall DJ, Ledingham JG, Warell DA. Oxford Text of medicine Vol. 1, 1986.

16. Smith T, Schellenbrg JA, Hayes R. Attributable fraction estimation and case definitions for malaria in endemic areas. State Med 1994; 13(22): 2345-58.

17. WHO Health organization. Advance in malaria chemotherapy report of WHO, Geneva 1984.

18. Warrell D A, Francis N. Malaria. In: Mcintyre N, Benhamou J P, Bircher J, Rizzetto M. Rodess J (editors) Oxford textbook of clinical hepatology Oxford: Oxford University Press; 1990. P. 70.

19. Malaria Action Program. Severe and complicated malaria. Trans R Soc Trop Med Hyg 1986; (suppl 8) 1- 50.

20. Saissy J M, Cellard P, Vitris F. Severe Malaria in an African seasonal endemic area. Comparison of aspects in adults and children and prognostic value of cytokines. Press Med J 1994; 15:23(31): 1426 –30.

21. Brule Chwatt L J (ed). Chemotherapy of malaria. In: Brule Chwatt L J (ed) Essential Malariology 2nd ed London: Heinemann Medical; 1981, WHO Monograph series No. 27. WHO Geneva 1985

22. Hommel M, David P, Oligine L. Surface alterations of erythrocytes in plasmodium falciparum malaria. Antigenic variation, antigenic diversity, the role of the spleen. Journal of Experimental Medicine 1983; 157: 1137 – 48.

23. Warrell D A, Francies N. Malaria. In: Mclntyre, N, Benhamon, T P Bircher, J Rizzetto M, Rodes J (editors) Oxford Textbook of clinical hematology, 2nd ed. Oxford: Oxford University Press; 1993. P. 101-7.

24. Brooks MH, Malpy JP, Bartelloni PJ, Tigertt WP, shechy T.W, Barry KG. Pathophysiology of acute falciparum malaria 1: Correlation of clinical and biochemical abnormalities, Am J Med 1967; 35:735-44.

25. Slutsker L, Chitsulo L, Macheso A, Steketee R W. Treatment of malaria fever episodes among children in Malaria: results of a KAP survey. Trop Med Parasitol 1994; 45(1): 61- 4.

26. Allen S J, O'Donnell A, Alexander N D, Clegg J B. Severe malaria in children in Papua New guinea Q J M 1996; 89(10): 779 – 88.

27. In Gerd Rooth and Anders Bjorkman. Fever episodes in a holoendemic malaria area of Tanzania: Parasitology and clinical findings and diagnostic aspects related to malaria Tran Rox Trop Med Hyg 1992; 47: 482.

28. Granham HA, Boxlan CW, Caroll G L, Sutera S, Williamsen J R, Gluzman I Y, Krogstad P J. *Plasmodiun falciparum* maturation obctishes physiologic red cell deformability Science 1984; 223: 400 –2.

29. Raventos-Suares, C Icaul, D K Macaloso F, Nagel R L. Membrane knobs are required for the micro- circulatory obstruction induced by *Plasmodium falciparum* – infected erythrocytes. Proceedings of the national academy of sciences of the USA 1985; 82:3829-33.

30. Igarashi I G, Shanly H, Reese R, Aikawa M. Knob antigen deposition in cerebral malaria. Am J Trop Med Hyg 1987; 37 (3): 511-5.

31. Lee MV, Ambras JC, De Souza J M, Lee R V. Diminished red blood cell deferability in uncomplicated human malaria A preliminency report. Journal of Medicine 1982; 13: 479 – 85.

32. Abdallah S, Weatherall DJ, Awickramasingle SN, Hughes M. The anaemia of *Plasmodium falciparum* malaria. Br J Haem 1980;46:171-83.

33. Macpherson GG, Warell M J, White N J, Looarecsuwan S, Warell D A. Human cerebral malaria a quantitative ultrestructural analysis of parasitzed erythocyte 1985.

34. Traley K J, Beutler B, Lowry S F. Shock and tissue injury induced by recombinant human cachectin Science. 1986; 234: 470-74.

35. Bygbjerg IC, Ianny C. Septicaemia as a complication of *falciparum malaria*. Trans Roy Trop Med Hyg83:839-43.

36. Abdallah S, Weatherall D J, Awickramasingle S N, Hughes M. The anaemia of *Plasmodium* falciparum malaria. Br J Haem 1980;46:171-83.

37. White N J, Champan D, Watt G. The effects of multiplication and synchronicity of the vascular distribution of parasite in falciparum malaria. Tran Roy Soc Trop Med Hyg 1992;86:590-97.

38. Umotong A B, Amanor Boadu S D, Okerengwo AA, Hedo C C. Serum complemen levels in asymptomic plasmodium falciparum parasitaemic children. Trop Geogr Med 1994; 46(3): 139-7.

39. Ultrasturctural alterations of non- parasitized Red Blood Cells during anaemia – Applied Parasitology. 1993.

40. NG R C K, Suki W N. Treatment of acute renal failure. In: Acute renal failure, Brener B M & Stein J H (Editors). New York: Churchill living Stone, 1980; pp 229 – 73.

41. Schmidt P J, Holland P V. Pathogenesis of acute renal failure associated with incompatible transfusion. Lancet ii: 1967; 1169 – 72.

42. Kackburn CRP, Hensley WJ, Grant DK, Wright F B. Studies on intravascular hemolysis in man. Pathogenesis of initial stages of acute renal failure journal of clinical investigation 1954; 33: 825- 34.

43. Aikawa M, Jalabs G, Whitely HE, Igarashi I, Ristic M: Qlomeralopathy in squrrel monkeys with acute plasmodium falciparum infection. Am J Trop Med Hyg 1988; 88 (1): 7- 14.

44. De Marie W J N, Harris J S. Effects of magnesium sulfate on alterations in renal dynamics induced by intravenous hemoglobin- Am J Physiol 1955; 182: 251- 55.

45. Looareesuwan S, HO, M Wattenagoon Y, White N J, Warrel D A, Bannag O,Harinaswta T, Wyler D . Dynamic alternations in splenic function in falciparum malaria – New England Journal of Medicine 1987a; 317:675-79.

46. White N J, Charpan D, Watt B. The effects of multiplication and synchronicity of the vascular distribution of parasite in falciparum. Malaria. Tran Roy Soc Trop Med Hyg 1992;86:590-97.

47. Warrell D A, White N J, Veall N, Looareesuwan S, Chanthavenich P, Phillips R E, Karbwant J, Pangpae P. Cerebral anaerobic glycolysis and reduced cerebral oxygen transport – in human cerebral malaria lancet 1988; 2 (8610): 534 – 88.

48. Boonpackavig V, Boonpcknavig S, Udomsangpetch R, Niganat P . An immune fluorescent study of cerebral malaria. Arch Path Lab Med 1990; 114: 1028 – 34.

49. Macgraith B G, Fletcher A. the pathogenesis of Mammalian malaria. Advances in Parasitology 1972; 10: 49-75.

50. White N J, H O M. The Pathophysiology of malaria Advances in Parasitology 1992;31:83-173.

51. WHO (1990) Severe and complicated malaria; Tran Roc Trop Med Hyg 84 supplement.

52. LI QQ, Guo X, Jian H, Fan T, Huang W. Development state of plasmodium falciparum in the intradermal peripheral and medullary blood of patients with cerebral malaria. National Medical journal of churia 1988; 63: 692 – 93.

53. Davis TME, Krishna S, Looareesuwan S, et al. Erythrocyte sequestration and anaemia in severe falciparum malaria: analysis of acute changes in venest 1990; 80: 793 – 800.

54. Tandon N N, Kralsz U, Jamieson GA. Identification of glycoprotein I V (CD 36) as a primary receptor for platelet – collagen adhesion J biol Chem 1989., 264 : 7576-87 .

55. Panton L J, Leech J H, Miller L H, Howard R L Cytoadhrerence of palsmodium falciparum – infected erythrocytes to human metanema all lines correlates with surface OKM5 antigen. Infected and immunity 1978; 55:2754- 58.

56. WHO (1990) Severe and complicated malaria; Tran Roc Trop Med Hyg 84 supplement.

57. Newton C R, Marsh K, peshu N, Kirkham F. Kenya Medical research Institute, clinical research center, Kilifi, Kenya pediatr Neurol 1996; 15 (1): 41 –9.

58. Udeinya I A, Schmidt J A, Aikawa M, Miller L H, Gree I. Falciparum malaria – infected erythrocytes bind to cultured human. Endothelial cells – science 1981;2137:555-57.

59. David P H, handannetti S M, Leech J H, Gamage P, Medis K N. Rosetting : A new cytoadherence property of malaria – infected erythrocytes. Am J Trop Med Hyg 1988; 38: 289 –97.

60. Hudomsangech R, Wahlin B, carlson J, Berzins K, Torri M, Aikawa M, perlmann P, Walgreen M. plasmodium falciparum – infected erythrocytes from Spontaneous erythrocytes rosettes. Journal of Experimental Medicine 1989 b; 196: 1835 –40.

61. H O M, Davis T M E, Silamut K, Bunnag D, gWhite N J. Rosetter formation of plasmodium falciparum infected erythrocyates from patients with acute malaria – infect and immunol 1991 b; 59: 2135 – 39.

62. Handunnethic S M, David P H, Perera K L, Mendis R L, K N. Uninfected erythrocytes from Rosette around plasmodium Falciparum infected erythrocytes. Am J Trop Med Hyg 1989; 40: 115 – 18.

63. Macpherson G G, Warell M J, White N J, Looarecsuwan S, Warell D A. Human cerebral malaria a quantitative ultrestructuarl analysis of parasitized erthocyte 1985.

64.Dinarello C A, Mver J W.lymphokines. n Eng J M 1987; 317: 940 – 45. Grau G E, Piguet P F, Vassalli P, H. Involvement of tumours necrosis factor and other cytokines. In immune – mediated vascular pathology Y, International. Archives of allergy and applied immunology 1989; 88:34 –39.

65. Blick M, sherwin S A, Roseblum M, Gutterman J. Phase I study of recombinant tumor necrosis factor in carrier patients canter Research 1987; 47:2986-89.

66. Baired J K, Jones T R, Danudingo E W, et al. Age dependent acquired protection against plasmodium falciparum in people having two years exposure to hyper endemic malaria. Am J Trop Med & Gyg 1991; 45: 65 – 76.

67. Brasseur P, Agrapant M, Ballett J J, Druilhe P, Warrell M J, Tharavanij S. Impaired cell mediated immunity in plasmodium falciparum infected patients with high parasitaemia and cerebral malaria. Clini immunol and immunopatholo 1983; 27: 38 –50.

68. Luty A J, Mayomo J, Lekoulou F, Mshana R. immunological responses to soluble exoantigens to continuous intense infection. Am J Torp Med Hyg 1994; 51 (6): 720-9.

69. Chirakalwasan N, Kamol R, Letmaharit S, Perimann H, Perlmann P, Thaitong S. A longitudinal study of seroreactivities to a major blood sage antigen (PF 155/ RESA) of the malaria parasite plasmodium falciparum in anendemic area of thailand. Souther East Asian. J Trop Med Public Health 1994; 25(1): 25 –31.

70. A'al- Yaman, Genton F, Falk M, Anders R F, Lewis D, Hii J, Beck H P, Alpers M P. Humoral response to *Plasmodium falciparum* – infected erythrocyte surface antigen in a highly endemic area of pupua New Guinea. Am J Trop Med Hyg 1995; 52(2): 66-71.

71. Nnalue N A, Friedman M J. Evidence for a neurotophil – medicalted protective response in malaria parasite immunology P J Trop Hyg. 1988; 10: 47- 58 .

72. HGM, Websler HK, Been B, Looareeuwan S, Kongchareoh S, White N J. Defective production of and response to interleukin 2 in a bite falciparum malaria. J immunol 1988; 141: 2755 –59.

73. Granham PCC. The role of the spleen in protocol infections with special reference to splenectomy acta tropica 1970; 27:1-24.

74. Pasvol G, Weatherall D J, Wilson R J M, Smith DH, Gilles H M. Fetal haemoglobin and malaria lancet I 1976; 1269-72.

75. Slutsker L, Taylor T E, Wirima J J, Stekette R W. In hospital morbidity and mortality due to malaria – associated severe anaemia in two area of malaria with different patterns of malaria infection. Trans Roy Soc Trop Med Hyg 1994;88(5): 548 – 51.

76. Li q q , Guo X, Jian H, Fan T, Huang W. Development state of plasmodium falciparum in the intradermal peripheral and medullary blood of patients with cerebral malaria – national medical journal of china 63, 692 – 93.

77. Molyneux M E, Talor T E, Wirima JJ, Borgstein J. Clinical features and prognostic indications in paediatric cerebral malaria – a study of 131 comatose Malawian children – Quart J Med 1989; 71: 441- 59.

78. Newton C R, Chokwe T Schellenberg J A, Winsterley P A, Forster O, Peshu N, Kirkham F J, Marsh K. coma scales for children with severe falciparum malaria. Trans R Soc Trop Med Hyg 1997.

79. Fisher CSW. Acidosis and hypoglycaemia in malaria 1986; 401 – 02.

80. Taylor T E, Molyneax M E, Wirima JJ, Fletcher K A, Morris K. Blood glucose levels in Malawian children before and during the administration of intravenous quinine for severe falciparum malaria.

81. New Eng. Journal of Medicine 1988; 319: 1040 –47. Carme N, Bouquety J C, Plassart H. Mortality and sequalae due to cerebral malaria in African children in Brazzaville, Congo. Am J Trop Med Hyg 1993; 48 (2): 216 – 21.

82. Krishna S, Waller D W, Ter Kuile F, et al. Lactic acidosis and hypoglycaemia in children with severe malaria: pathophsiology and prognostic significant. Trans Rox Trop Med Hyg 1994; 88 (1): 67 – 78.

83. Marsh K, Foster D, Waruiru C,et al. Indicators of life threatening malaria in African children. N Engl. J Med 1995; 332 (21): 1399 – 404.

84. Bennish M l, Azad A K, Rahman D, Phillips R E. Hypoglycaemia duting diarrhoea in cildhood. New Engl. J Med 1990; 332: 1357 –60.

85. Wernsdorfer W H, Mc Grezor I A .Text book of Malaria Churchill living stone Edinburgh (in press) 1986.

86. Crawley J, Smith S, Kirhham F, Muthinji P, Waru C, Marsh K, Seizures and Status epilepticus in childhood cerebral malaria. QJM 1996; 89(8): 591 –7.

87. White N J, Miller K D, Marsh K, Berry C D, Turner R C, Williamson D H,

Brown J. Hypoglycaemia in African children with severe malaria. Lancet, 1987a; I: 608-11.

88. Omanga U, Ntihinyurwa M, Shako D, Mashako M. less heiplegics all course de lacces pernicieux a plasmodium falciparum de lenfant, Annales de pediatric 1983; 30: 294 – 96.

89. Marsh K et al: indicators of life: Threatening malaria in African children. N Engl J Med 1499; J32”1399.

90. H O M, Webster H K, looareesuwan S, Supanovanond W, Phillips R E, Chanthavanich P, Warmell D A. Antigen Specific immunosppression in human malaria due to plasmodium falciparum. J Inf Dis 1986; 153: 763 –71.

91. Migasena S. Hypoglycaemia in falciparum malaria. Ann Trop Med Parasitol 1983; 77:323-24.

92. Mabeza G F, Moyo V M, Thuma P E, Biemba G, Parry D, khumalo H, Nyarugwe P, Zulu S, Gordeuk V R. Predictors of severity of illness on

presentation in children with cerebral malaria. Ann Trop Med Parasitol 1995; 89 (3) : 221 –8.

93. White N J, Krishnas. Treatment of malarea some considerations and limitations of the current methods of assessment. Tran Roy Trop Med Hyg 1989;83: 767-777.

94. Wattanagoon Y, Srivilairit S looareesuwan S,. Convulsions in childhood malaria trans R Soc Trop Med Hyg1994;88(4):426-8.

95. Greenwood B M, Bradly A K, Greenhood A M, Byass P, Jamneh K, March K, Tulloch S, Old field F S J, Hayes R. Mortality and morbidity from malaria among children in a rural area of the Gambia – West Africa. Tran Roy Soci Trop Med and Hyg. 1987;81:478-89.

96. Menon R. Pregnancy and malaria. Med J of Malys 1972; 27: 115 –19.

97. Berndin G, Fournier J P, Quaranta J F, Marty P, Dellamonia P, Mattei M. Syndrome de detresse respiratoire aigue d'evolution fatale a presxsoguiotrasfusion all cours d' unacces pernicieus palustre. La presse medicale 1989; 18: 1394-95.

98. Krishna S, Waller DW, Ter Kuite F, et al. Lactic acidosis and hypoglycamia in

children with severe malaria: Pathophysiological and prognostic significant. Tran

Roy Trop Md Hyg 1994; 88(1) :67-78.

99. Charoenlarp P, Vanijannta S, Chat panyaporn P. The effect of prednisolone on red cell survival in patients with falciparum malaria. Suoth East Asian J Trop Med and public Health 1979; 10,127-31.

100. Akpede G O, Sykes R M, Abiodum P O. Convulsions with malaria. Febrile or indicative of cerebral involvement ? J Trop Pediatr 1993; 39 (6) : 350 –5.

101. Schmidt P J, Holland P V. Pathogenesis of acute renal failure associated with incompalite transfusion.Lancet 1967; ii: 1169-72.

102. Sialmut K, White N J. Relation of the stage of parasite development in the peripheral blood to prognosis in severe falciparum malaria. Tran Roy Soc Trop Med Hyg 1993; 87 : 436 – 43.

103. White N J, Miller K D, churchill F C, Berry C D, Brown J, Williams S B, Greenhood B M. Chloroquine treatment of severe malaria in children: pharmacokinetic toxicity and new dosage recommendations. New Eng J Med 1988b;319: 1493-1500.

104. Thumwood C M, Hunt N H, Clarse I A. Comden W B: Breakdown of the blood brain barier. In murine cerebral malaria. Parasitology 1988;96:372-89.

105. Jaffar S, Van Hensbroek M B, Palmer A. Predictors of a fatal outcome following children cerebral malaria. Am J Trop Med Hyg 1997;57 (1): 20-4.

106. Abdulla M N, Sokrab M, Siddig H E. post malarial cerebeller ataxia in adult Sudanese patients East Afrecan Med J 1997-74(9): 40-8.

107. Al- Yaman F, Genton B, Anders RF. Relationship between humoral response to plasmodium falciparum merozoite surface antigen – 2 and malaria morbidity in a highly endemic area of papua New Guinea. Am J Trop Med Hyg 1994; 51(5): 3939 –602.

108. Gilles H M, Fletcher K A, Hendrickse R C, Linder R, Reddy S, Allan N. Glucose – 6- Phosphate dehdyrogenase deficiency, sickling and malaria in African children in Southern Western Nigeria. Lancet 1967; 138- 40.

109. Wezam A.Malaria survey at humera north western Ethiopian-Ethiop-Med-J-1994;32(1): 41-7.

110. Bassett M T, Taylor P, Bvirakare J, Chiteka F, Govere E. Clinical Diagnosis of malaria. Can we improve ? J Trop Med Hyg 1991; 94: 65 – 69.

111. Genton B, Smith T, Bala K, Narata A, Al – Yaman F, Beck H P HIT J, Alpers M. Malaria. How useful are clinical criteria for improveing the diagnosis in highly endemic area ? Tran Roy Tro Med Hyg 1994; 88: 537 –41.

112. Sialmut K, White N J. Relation of the stage of parasite development in the peripheral blood to prognosis in severe falciparum malaria Tran Roy SocTrop Med Hyg1993;87:436-443.

113. Ward K N, Wamell M J, Rodes J, Looreesuwan S, White N J.Alered expression of human monocyte F C receptor in *Plasmodium falciparum* malaria infection and immunity 1984; 44:623-626.

114. Thumas upapong s, Tin T, sukontason k, sawaaddichi c karbwang J. Electroencephalograph in cerebral malaria southeast Asian. J Trop Med Public Health. 1995; 26(1):34-7.

115. looreesuwan s, Wilairatana p, Krishna s, Kendall B, Vannaphan S Virvan C, White NJ. Magnetic resonant imaging of the brain in patients with cerebral malaria. Clininfect Dis 1995; 21 (2): 300-9.

116. White NJ, Warrell DA, Chanthavanich P, Looareesuwan S, Turner RC. Severe hypoglycaemia and hyper insulinaemia in falciparun malaria. N. Eng J. Med. 1983 a; 309:61-66.

117. Thumwood C M, Hant NH, Clark I A, Comden W B. Bbreak down of the blood train barrier in murise cerebral malaria parasitology 1988; 96: 372- 89.

118. Tange P A, Dreschler W A, Claessen R M, Ototoxic reactions of quinine in healthy persons and patients with plasmodium falciparum infection. Auris Nasus Larynx, 1997;(8): 160-77.

119. Ward K N, Warrell M J, Looreesuwan S, White N J. Altered expression of human monocyte FC receptor in *Plasmodium falciparum* malaria infection and immunity 1984; 44:623 – 626.

120. Looarecsuwan S, phillips RE, White NJ. Intravenous amodiaquine and oral amodiaquine –erythromycin in the treatment of chloroquine resistant *Falciparum malaria*. Lancet 1985b u:805-8.

121. Watkins WM, Sixmith DG, Spencer HC, Boriga DA, Kariuki DM, Kipingor T, Kocch DK. Effectiveness of a modiaquine as treatment for chloroquine –resistant *Plasmodium falciparum* malaria in Kenya. Lancet 1984; i : 357-59.

122. Hashim M sir K, Omer S, Elrayis M A, Mohamed H E B. The clinical pattern and outcome of cerebral malaria in children Khartoum – Sudan association of physicians 15th conference, 19-21 March 1996.

123. Migasena P, Maegraith B G . Pharmacological action of antimalarial drugs action of chloroquine and hydrocortisone on blood brain banier. In: *Plasmodium knowlesi malaria*. Transaction of the Roy Soc Trop Med Hyg 1967; 61 :6.

124. Looareesuwan S, phillips RE, white N J,Karbwang J, Berjasurat Y, Kasemsarn P, Warrell D A, Attanath P. intravenous a modiaquine and oral a modiaquine- erythromycin in the treatment of chloroquine resistant *Falciparum malaria*. Lancet 1985a; 805-8.

125. Hatton C S, peto T E A, Bunch C, pasvol G, Russell S J, Singer C, Edwards G, Winstanley P. Frequecyof severe neutropenia associated with a modiaquine prophylaxis against malaria. Lancet 1986; I: 411- 14.

126. Neflet K, Woodthy W, Schmidt R, Frisch P, Fehr J. Amodiaquine induced agranulocytosis and liver damage. Br Med J 1986; (292) 722: 721-23.

127. Prien Larsen J C, Stjernquist M. Malaria in pregnancy –a master of masquerade. Acta Obstet Gunecol Scand 1993;72 (6):496-7.

128. White N J, Warrell D A, Looareesuwan S, Chanthavanich S, Phillips R E, Pongpaew P. Patholphysiological and pergnostic of cerebrospinal fluid lactate in cerebral malaria- lancet 1985;I:776-78

129. Ter –Kuile Fo, Nosten F, Luxemburger C, et al, Mefloquine treatment of acute *Falciparum malaria*. White N J 1995;73(5):631-42.

130. Ahmed R A, Rogers H J. Pharmacokinetics and protein binding interactions of depsene and pyrimethamine. Br J Clin Pharmacol 1980;10:519-24.

131. Mohanty S, Mishra SK, Satpathy SK, Dash S, Patnaik J. Alpha, Beta– Arteether for the treatment of complicated *Falciparum malaria*. Tran R Soc Trop Med Hyg 1997; (3): 328-30.

132. Taylor TE, Wills BA, Kazembe P, Chisale M, Wirima JJ, Ratsmi EY, Molyneux M E. Rapid coma resolution with artemether in Malawian children with cerebral malaria. Lancet.1993; 341(8846):764-50.

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