

Subclinical Hypothyroidism and Later Overt Hypothyroidism in Plasmodium Falciparum Malaria Infection.

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Abstract:

Background : Malaria one of the most complex infectious disease with varied type of clinical presentation and challenge for treatment. In this study few cases with plasmodium falciparum malaria infection are showing Biochemical subclinical hypothyroidism and overt hypothyroidism .Studies of these cases with complete blood count and peripheral smear provide an opportunity to visualise various stages of Malarial parasites infecting RBC and concurrent examination with T3,T4 and TSH provide to know the function of thyroid gland. This Article was written to evaluate the patients with subclinical hypothyroidism for Plasmodium falciparum malaria. Rigorous treatment for plasmodium falciparum malaria parasite may prevent cases from associated morbidity like hypothyroidism. Since there were no studies comparing malarial parasites seen in peripheral smear and biochemical changes in thyroid hormones and complete haemogram we have taken up this study to evaluate cases of slide positive malaria with subclinical hypothyroidism.

Materials and Methods: We have assessed T3,T4and TSH and complete blood count with Peripheral smear examination in 100 cases having fever and myalgia between 2016 and 2019.

Among them 20 cases showed normocytic normochromic blood picture 40 cases showed microcytic hypochromic anaemia and 40 cases showed microcytic hypochromic anaemia with thrombocytopenia in complete blood count on further evaluation with peripheral smear plasmodium falciparum parasites were detected in these 40 cases of microcytic hypochromic anaemia with thrombocytopenia .All these 40 cases with microcytic hypochromic anaemia with thrombocytopenia and plasmodium falciparum malaria were evaluated for thyroid hormones.

Results: Increased level of Thyroid stimulating hormone were seen in 4 cases with T3 and T4 within normal limits and hence cases were considered has subclinical hypothyroidism. All the slide positive plasmodium falciparum cases were treated with antimalarial drugs.

After three month, follow up result showed parameters of complete blood count within normal limits and slides were negative for plasmodium falciparum malaria parasite. One case on follow up forthyroid hormone analysis showed normal T3decreased T4 and increased TSH indicating overt hypothyroidism and was started on thyroxine hormone replacement therapy

Conclusion : The detection of gametocytes, Trophozoites, schizonts of plasmodium falciparum species in peripheral smear examination in the cases studied having fever, myalgia, microcytic hypochromic anaemia with thrombocytopenia and plasmodium falciparum infection as ascertained that one of the causative factor for the depressed function of thyroid gland in cases diagnosed with subclinical hypothyroidism and overt hypothyroidism in our study is malarial infection.

Key Words : Fever; Anaemia; Thrombocytopenia; Plasmodium Falciparum Malaria; Thyroid Stimulating Hormone; Subclinical Hypothyroidism; Overt Hypothyroidism.

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I. Introduction:

Subclinical hypothyroidism is defined as a serum thyroid stimulating hormone(TSH) level above the upper limit of normal despite normal levels of serum free thyroxine ^{1,5}.Subclinical hypothyroidism, defined as an elevated serum thyrotropin (Often referred to as thyroid-stimulating hormone, or TSH)level with normal levels of free thyroxine(FT4)affects up to 10% of the adult population².Recent data from Africa suggest that severe malaria is commonly misdiagnosed, leading to a failure to treat other causes of life threatening disease³ .Making a definite diagnosis of severe malaria in disease- endemic areas is complicated by the fact that

parasitemia may be incidental to other concurrent severe disease. In areas of high transmission, the prevalence of asymptomatic parasitemia in the population may be as high as 40-70%^{4,6} and the signs of severe malaria are nonspecific. Abnormal thyroid function is strongly associated with mortality in severe non thyroidal illness⁹. Thyrotroph and thyroid gland function are depressed during acute, severe malaria. As these changes may be an adaptation to accelerated catabolism⁹. Hence this study was taken to make correlation between fever, myalgia, anaemia, thrombocytopenia, and plasmodium falciparum malaria and subclinical hypothyroidism later few cases to be overt hypothyroidism.

II. Materials And Methods:

This prospective correlative study was carried out on patients at Pathology and blood disorder Laboratory at Chigateri District Hospital, Jagadguru Jayadeva Medical College, Davangere, Karnataka State, INDIA from January 2016 to November 2019. A total of 100 patients/cases were in this study.

Study Design: Prospective correlative study

Study Location: This study was done in secondary care District teaching hospital in Pathology and Blood disorder laboratory at Chigateri District Hospital, Jagadguru Jayadeva Murugharajendra Medical College, PJ Extension, Davanagere Karnataka State, INDIA.

Study Duration: January 2016 to November 2019

Sample size: 100 Patients

Sample size calculation: Random case samples received at Pathology and Blood disorder Laboratory.

Subjects & Selection method: The study was done from Patients blood samples received at Pathology and blood disorder laboratory. Blood sample received was 2ml EDTA Blood in lavender cap vacutainers and 5ml of blood in red cap vacutainers from patients with chief complaints of Fever, myalgia and complete haemogram report suggesting Anaemia with Thrombocytopenia were studied, and peripheral smear study using Leishman stain was done and studied simultaneously all 100 cases were subjected to Thyroid stimulating hormone, Tri iodothyronine and Tetra iodothyronine hormone analysis.

Inclusion criteria:-

1. Patients with Fever, myalgia, Complete haemogram report with anaemia and thrombocytopenia with peripheral smear report of positive plasmodium falciparum malaria parasite.
2. Either sex
3. Any age

Exclusion criteria:

1. Hemoglobinopathies
2. Known cases of hypothyroidism on treatment
3. Known cases of subclinical hypothyroidism on follow up
4. Cases with blood transfusion 3 months prior to sample study,
5. Haemolysed samples
6. Thyroid antibody test positive

Procedure and Methodology:

Written informed consent from patients was obtained. Laboratory requisition forms were obtained from clinicians. Details taken from requisition forms were sociodemographic characters like Age, gender, address, nationality, date and time of sample collected, type of sample collected, brief clinical history of patient was noted 2ml EDTA venous blood obtained was run in 5 part haematology analyser and peripheral smear slides were prepared using the same sample and stained with Leishman stain with 6.8 PH buffer and detailed slide study was made and appropriate photos of malarial parasites were captured using mobile camera.

At the same time 5 ml whole blood was collected in red capped vacutainer for thyroid hormone like T3, T4, and TSH Analysis.

Statistical analysis:

From 100 cases with fever and myalgia, totally 200 samples were analysed, two sample each from one patient I.e. 2ml EDTA anticoagulated blood for complete haemogram and 5 ml plain whole blood for thyroid hormones. 20 samples reported as having normocytic normochromic blood picture. 40 cases were having Microcytic hypochromic anemia. Remaining 40 cases were reported microcytic hypochromic anaemia with thrombocytopenia and malarial parasite positive. Parasites detected were of plasmodium falciparum species in various stages like Gametocytes, trophozoites and schizonts. All the 40 malaria positive cases were put on treatment for plasmodium falciparum malaria. 4 cases were reported with increased Thyroid stimulating hormone and within normal limit triiodothyronine and tetra iodothyronine after three months follow up result of these 4 cases showed one case with increased TSH and tetra iodothyronine. Analysed DATA showed 40% of fevers with myalgia cases were plasmodium falciparum malaria positive, in them 4% of cases suffered subclinical hypothyroidism and 1% of case suffered overt hypothyroidism. In cases treated for plasmodium malaria 10% of cases suffered subclinical hypothyroidism and 2.5% of cases suffered overt hypothyroidism

III. Results:

After complete malarial treatment 3 months follow up of all 100 cases for symptoms, complete haemogram with peripheral smear, thyroid hormones analysis was done. Among which four cases which showed increased thyroid stimulating hormone before anti malarial treatment three cases reverted to normal TSH Value, but one case showed persistent increased TSH and T₄ Value.

Table no.1: Shows study of complete hemogram with peripheral smear for 100 cases with 20 cases showing Normocytic normochromic blood picture, 40 cases showing microcytic hypochromic Anaemia, 40 cases showing microcytichypochromic anaemia with thrombocytopenia and plasmodium falciparum malaria parasites.

<i>Serial number</i>	<i>Complete haemogram with peripheral smear report</i>	<i>Total Number of Patients</i>
1	<i>Normocytic Normochromic blood picture</i>	20
2	<i>Microcytic Hypochromic Anaemia</i>	40
3	<i>Microcytic Hypochromic Anaemia with thrombocytopenia and Malarial parasite positive</i>	40
	<i>Total number of cases</i>	<i>100</i>

IMAGES OF MALARIAL PARASITE

Figure1: Growing trophozoite in enlarged red blood corpuscles with chromatin division

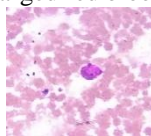


Figure 2: Presegmenting Schizont

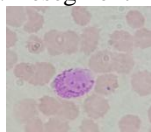


Figure 3: Rupture schizont

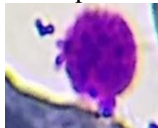


Figure4: Mature Schizont



Figure 5: Immature Gametocyte Successive forms in the development of Gametocytes

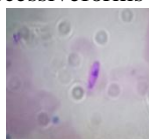


Table no.2: Shows among 100 cases studied for Thyroid stimulating hormone, Triiodothyronine, Tetraiodothyronine hormones 96 cases showed hormones within normal limits and 4 cases showed increased Thyroid stimulating hormone with tri iodothyronine and tetraiodothyronine in normal limits.

Number of samples tested	Sample with normal TSH Value	Sample with increased TSH Value	Sample with normal T ₃ value	Sample with normal T ₄ Value
100	96	4	100	100

TABLE no.3: Shows Dosage schedule of Artemisinin Combination Therapy (ACT) AS+SP and PQ for Plasmodium Falciparum malaria¹⁰ AS-artesunate, SP-sulfadoxin –pyremethamine

Age group (years)	1 st day	1 st day	2 nd day	2 nd day	3 rd day
	AS	SP	AS	PQ	AS
0-1	1(25mg)	1(250mg+12.5mg)	1(25mg)	Nil	1(25mg)
1-4	1(50mg)	1(500mg+25mg)	1(50mg)	1(7.5mg base)	1(50mg)
5-8	1(100mg)	1(750mg+37.5mg)	1(100mg)	2(7.5mg base each)	1(100mg)
9-14	1(150mg)	2(500mg+25mg each)	1(150mg)	4(7.5mg base each)	1(150mg)
15&above	1(200mg)	2(750+37.5mg each)	1(200mg)	6(7.5mg base each)	1(200mg)

Figures in parentheses indicate doses and outside the parantheses number of tablets

Table no.4: Shows follow up results of four cases after completing malarial treatment at third month. All four cases were plasmodium falciparum malarial slide negative along with no fever and myalgia, and anaemia

Number of Samples	Fever	Myalgia	Complete haemogram within normal limits	Slide positive plasmodium falciparum malaria
4	NIL	NIL	4	NIL

Table no.5: Shows follow up results of four cases after completing malarial treatment at third month for thyroid hormones where one case showed increased TSH (thyroid stimulating hormone) and remaining three cases showed thyroid hormone results within normal limits

Number of sample tested	Sample with normal TSH Value	Sample with increased TSH Value	Sample with normal T ₃ value	Sample with normal T ₄ value	Sample with increased T ₄ value
4	3	1	4	3	1

All 4 subclinical cases were reviewed with clinical history, complete haemogram and thyroid hormone analysis. All four cases had no h/o fever/myalgia .One case report was showing increased Thyroid stimulating hormone and tetra iodothyronine and triiodothyronine within normal limits indicating overt hypothyroidism.

IV. Discussion

Subclinical hypothyroidism or thyroid failure is a common problem with a prevalence of 3% to 8% in the population without known thyroid disease.^{11, 12}

Patients with subclinical hypothyroidism have a high rate of progression to clinically overt hypothyroidism 2.6% each year if thyroperoxidase (TPO) antibodies are absent and 4.3% if they are present.¹³ However, some persons do not show progression and some experience normalization.

A TSH level greater than 10mIU/L predicts a higher rate of progression, and a level of less than 6mIU/L predicts a lower likelihood of progression. A study in men and women older than 55 years with a mean follow up of 32 months the TSH level normalised in 52% of those with a serum TSH of less than 10mIU/L¹⁴

In our case study we have come across 4 cases of subclinical hypothyroidism in 40 cases infected with plasmodium falciparum malaria and in that 4 cases developed subclinical hypothyroidism and later one case was overt hypothyroidism after 3 month follow up. The Government of INDIA as to reassess the national malaria elimination programme and also study in detail the morbidity associated with plasmodium falciparum malaria and prevent the patient from developing hypothyroidism.

In May 2015, the World Health Assembly endorsed a new Global technical strategy for Malaria 2016-2030, setting ambitious goal aimed at dramatically lowering the global malaria burden over this 15-year period, with milestones along the way to track progress. A key milestone for 2020 is the elimination of malaria in at

least 10 countries that had the disease in 2015. To meet this target, countries must report Zero indigenous cases in 2020¹⁵. At present, malaria can only be labelled if a positive blood smear is documented (based upon the WHO definition of malaria). Therefore, patients who live in a malaria area who though reporting with all the signs and symptoms of malaria and /or have positive rapid diagnostic test (RDT) cannot be labelled as malaria unless a positive blood smear is documented. Moreover, the patients who do not go to the designated health centre or prefer other health system or facilities in public or private sector cannot be captured by the surveillance system. In view of this, it may be considered worthwhile to designate malaria as a notifiable disease, thereby making reporting of malaria cases mandatory for all private and public health facilities in the country.¹⁶ Accordingly the World Health Assembly should consider depressed thyroid function as one of the morbidity associated with plasmodium falciparum infection and intensify its detection and treatment aspects regarding malaria.

V. Conclusion

Detection of plasmodium malarial parasite in fever cases and treating them appropriately significantly reduces global burden of Subclinical hypothyroidism and later overt hypothyroidism and prevent many hypothyroid patients with thyroid hormones treatment.

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