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Multiple Endocrine Dysfunctions in Adult Severe Falciparum Malaria

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Abstract

Introduction: Severe falciparum malaria causes multiple organ dysfunction with different grades of severity that cause death. In this study we investigate multiple endocrine gland dysfunction in severe falciparum malaria and its impact on outcome.

Material and Methods: 162 patients of severe and 43 patients of uncomplicated falciparum malaria (UM) were included. The diagnosis of malaria was done either with the detection of asexual form of the parasite in the peripheral smear or by Rapid diagnostic test. On admission blood was collected for estimation of serum cortisol, T3, T4, TSH, parathormone, Vit-D, Calcium, phosphate, and Insulin in addition to hematological and biochemical investigations. Insulin resistance and beta cell function were assessed by HOMA model.

Results: This study showed low cortisol (18.3±1.7µg/dl), low T3 (76.1±21.4 ng/ml), hypocalcemia (8.2±3.6 mg/dl), hypophosphatemia (2.5±0.7mg/dl), low vitamin D (27.8±13.6 ng/ml) and low level of parathormone (5.4±2,8 pg/ml). There is insulin resistance with beta cell dysfunction. These values are further lower among patients who died.

Conclusion: The present study showed that severe falciparum malaria causes multiple endocrine dysfunction that affect the outcome adversely.

Keywords: Cortisol Insufficiency; Sick-Euthyroid State; Insulin Resistance; Hypovitamonosis-D

Abbreviations: SM: Severe Malaria; MODS: Multi Organ Dysfunction Syndrome; RDT: Rapid Acting Test; MSS: Malaria Severity Score; PT: Prothrombin Time; CIRCI: Critical Illness-Related Corticosteroid Insufficiency; RAI: Relative adrenal insufficiency.

Introduction

Human malaria is a parasitic disease caused by five different species of Plasmodia, of which *P.falciparum* is most common and notorious. In less than 1% of cases it progressed from clinically mild disease to severe malaria (SM) causing multi organ dysfunction syndrome (MODS) and resulting death in about 15-25% patients [1,2]. The pathogenesis of severe falciparum malaria (SM) is multifactorial that include activation of innate immunity, endothelial dysfunction, and enhanced coagulation along with sequestration of parasitized RBCs3. All these cause several complications that lead to MODS [2,3]. Endocrine dysfunction has been recognized in sepsis complicated with MODS and its role in pathogenesis and prediction of outcome has been document [4]. Further, hormones act like cytokines during inflammation that lead

to sepsis and for this action, hormones are also named as "hormokine" [5]. Procalcitonin (PCT) has been considered as the prototype of hormokine [5]. High PCT, relative adrenal failure, sick euthyroid syndrome have been detected among patients with sepsis and SM affecting the outcome adversely [6]. Therefore, we have undertaken this prospective study to find out different endocrine dysfunctions in SM and its role in the outcome of disease.

Material and Methods

This study is a single center prospective study on complicated malaria conducted at VSS Institute of Medical Sciences and Research (VIMSAR), Burla, Odisha. Consecutive adult patients of falciparum malaria with various complications admitted to Department of Medicine from January 2010 to December 2016 were included in this study.

The diagnosis of malaria was made either with detection of asexual form of *P.falciparum* from Giemsa stained peripheral blood smear or rapid acting test (RDT). SM was diagnosed according to the guidelines of World Health Organization [1]. Organ dysfunction and its severity were assessed with Malaria Severity Score (MSS) [2]. The sample size was estimated by n.Master version 2.0 [7]. Patients with diseases like diabetes mellitus, chronic renal failure, chronic liver disease, rheumatic heart disease, coronary artery disease, and associated infections like pneumonia, urinary tract infection and viral hepatitis were excluded from the study.

Detailed history, physical examinations were recorded in a proforma. On admission, peripheral blood smear was collected for Giemsa staining on admission to assess parasitaemia. Blood was collected for estimation of glucose, urea, creatinine, sodium, albumin, bilirubin, aspartate amino transferase, alanine amino transferase, and for CBC, and prothrombin time (PT). Cerebrospinal fluid analysis, abdominal ultrasound, chest X-ray and serological markers for viral hepatitis were done to exclude the patients as described in exclusion criteria. Blood was collected for estimation of cortisol, T3, T4, and TSH, Vitamin-D, parathormone, Calcium, phosphate, and Insulin assay. Insulin resistance and beta cell function was calculated from HOMA model. HOMA-R= Insulin × Fasting blood Glucose (FBG) /405 and HOMA-B = Insulin×360/ (FBG-63) [8]. When we could not collect the blood at the time of admission, it was collected next day at 8 A.M. Care had been taken not to administer intravenous dextrose solution and lipid before collection of blood sample.

Serum 25 (OH) D concentration ≥30 ng/ml was considered normal and <20 ng/ml was defined as Vit-D deficiency [9]. Serum cortisol level <3.0 µg/dl and < 8.0 µg/dl has been considered as adrenal insufficiency (AI) and relative adrenal insufficiency (RAI) [10]. The different hormones were estimated with Chemiluminescence immunoassay. All patients were treated with injection Artesunate 2.4 mg/kg at 0 hrs., 12 hrs., 24 hrs. then once daily for 7 days or continued until they were able to tolerate drugs orally according to WHO guidelines [11]. Supportive treatment was given as per requirement. Statistical analysis was done by SPSS version [11]. Mean and SD were calculated. Students t test was used for comparison between values of two groups. We performed univariate analysis to realize the association between mortality and each endocrinological predictor.

Results

Out of 162 patients of falciparum malaria, there were 117 (72.2%) patients with SM and 45 (27.7%) patients with uncomplicated falciparum malaria (UM). We have taken 30 patients without malaria as normal control for endocrinological investigations. Of 117 patients of SM 76 (64.9%) were male and 41 (35.1%) were female. There was a male predominance in this study group with the ratio M:F=4:1, and majority of males were in the 21 to 40 years of age group; most of the females were in 41 to 50 years of age group. Out of 117 patients of SM single organ involvement was found in 50 (42.7%) patients and multi-organ involvement was found in 67 (57.2%) patients. Hepatic failure was the most common organ system failure (n=58; 49.6%), followed by neurological (n=50;42.7%) ,renal (n=40;34.1%), hematological (n=30; 25.6%), and, respiratory failure (n=15; 12.8%). Two, 3, 4, and 5 organ dysfunctions constituted 14 (11.9%), 32 (27.3%), 14 (11.9%), and 7 (5.9%) patients, respectively. Cerebral malaria, hepatic, and renal involvement was the most common combination of organ dysfunctions found in this study (27.3%). The T3 level in SM (76.1±21.4 ng/ml) was lower than controls (111.4±11.4 ng/ml) and UM (108.2±12.8 ng/ml) p<0.001. T4 level among patients of SM (8.1±3.2 µg/dl) is lower than control (9.4±1.6 µg/dl) but not statistically significant (p=0.5). TSH was also lower in SM (2.9±1.5 µIU/ml), than control (3.9±0.6 µIU/ml, p=0.5) (Table 1). FBG among patients with SM was higher (145.8±21.7mg/dl) along with high HOMA-R (7.4±3.4) and low (27.8±11.0) HOMA-B. In normal control HOMA-R and -B was 0.8±0.2 and 98.8±11.9. Parathyroid axis showed hypocalcemia 8.2±3.6 mg/dl, hypophosphatemia (2.5±0.7 mg/dl), and low (35.1±21.9 pg/ml) PTH. Serum Vit-D level among controls (41.1±14.4 ng/ml) and UM (40.7±16.0 ng/ml) was not different significantly (p=0.5), hence comparable and it was significantly less among patients with SM (27.8±13.6 ng/ml, p<0.001) (Table 1).

Investigations	Normal Control	UM (n=43) Mean ± SD	SM (n=117) Mean ± SD	SM (Death, n=12) Mean ± SD	P value
FBS (mg/dl)	77.5 ± 11.4	82.5 ± 12.5	145.8 ± 21.7	125.8 ± 11.5	0.001/0.5
Fasting Insulin (µIU/ml)	4.1 ± 0.8	5.2 ± 1.8	11.9 ± 5.9	9.9 ± 2.6	0.001/0.01
HOMA-R	0.8 ± 0.2	2.2 ± 1.1	7.4 ± 3.4	8.4 ± 5.2	0.001/0.5
HOMA-B	98.8 ± 11.9	40.8 ± 19.5	27.8 ± 11.7	24.6 ± 1.6	0.001/0.01
T3 (ng/dl)	111.4 ± 11.4	108.2 ± 12.8	76.1 ± 21.4	46.9 ± 9.3	0.001/0.001
T4 (µg/dl)	9.4 ± 1.6	9.1 ± 1.3	8.1 ± 3.2	7.9 ± 1.2	0.5/0.5
TSH (µIU/ml)	3.9 ± 0.6	3.4 ± 0.9	2.1 ± 1.5	1.9 ± 0.5	0.5/0.5
S. Calcium (mg/dl)	10.2 ± 2.5	9.1 ± 1.3	8.2 ± 3.6	6.2 ± 1.6	0.01/0.01
S. phosphate (mg/dl)	3.8 ± 1.9	3.1 ± 1.2	2.5 ± 0.7	2.1 ± 0.1	0.001/0.5
PTH (pg/ml)	55.1 ± 61.7	52.5 ± 45.2	35.1 ± 21.9	32.6 ± 11.7	0.001/0.01
Cortisol (µg/dl)	38.6 ± 7.5	35.6 ± 8.8	18.3 ± 1.7	5.3 ± 1.8	0.001/0.001
Vitamin D (ng/ml)	41.1 ± 14.4	40.7 ± 16.0	27.8 ± 13.6	22.8 ± 13.6	0.001/0.01

Table 1: Endocrinological parameters in different groups of falciparum malaria (all subjects).

The mean serum cortisol level was 18.3±1.7µg/dl which was significantly lower than control 38.6±7.5 µg/dl (p<0.001). However, in 80 (68.3%) patients, S. cortisol was below 8.0mg/dl with an average of 6.3±1.7 µg/dl and diagnosed RAI. In one patient (0.8%) the cortisol level was 2.8 µg/dl suggestive of primary adrenal failure. Out of 117 patients of SM there were 12 (10.2%) deaths. Among them, the mean serum cortisol, T3, serum calcium, Vit-D, PTH were 5.3±1.8 µg/dl, 46.3±9.3 ng/ml, 6.2±1.6 mg/dl, 22.8±13.6 ng/ml, 32.6±11.7 pg/ml respectively and were statistically significant (p<0.001). Low cortisol, low T3, low calcium, low Vitamin-D, are found as bad prognostic factors (Tables 2 & 3).

Variable	Wilk's Lambda	F	Significance
Sex	0.99	0.24	0.61
Age	0.98	0.78	0.39
Malaria Severity Score	0.76	22.37	0.0001
Cortisol	0.44	91.27	0.0001
T3	0.97	1.74	0.002
T4	0.7	5.9	0.24
TSH	0.96	1.58	0.214
FBG	0.96	2.62	0.001
FIA	0.99	0.001	0.972
HOMA-R	0.91	7.01	0.019
MOMA-B	0.96	2.37	0.127
S. Calcium	0.99	2.62	0.001
S. Phosphate	0.97	1.48	0.226
S. PTH	0.97	2.36	0.128
S. Vit-D	0.97	2.64	0.001

Table 2: Wilk's lambda (U-statistics) and Univariate 'F' ratio in Discriminant analysis.

Variable	Walk's Lambda	F	Co-efficient	P value
Cortisol	0.44	91.27	0.38	0.0001
MSS Score	0.76	22.37	0.21	0.0001
T3	0.97	1.74	0.02	0.002
S.calcium	0.99	2.62	0.11	0.001
Vit.D	0.97	2.64	0.12	0.001

Table 3: Summary of discriminant analysis

Discussion

The current study showed that SM is not only a multi organ disease but also a pan-endocrine illness causing dysfunction of multiple endocrine glands. It showed that adrenal failure, sick-euthyroid syndrome, insulin resistance and B-cell dysfunction, Vit-D deficiency and parathyroid dysfunction causing hypocalcemia, hypophosphatemia were present in patients of SM. Patients with SM may have primary or secondary AI. The former is due to affection of adrenal cortex because of necrosis or impaired circulation due to sequestration of parasites and was found in 1 (0.8%) case. The later is due to altered set point for cortisol inhibition of ACTH or erythrocyte sequestration within the hypothalamic-pituitary portal system and is found in 68.3% cases [10,12]. The parasites also produce a peptide like mammalian somatostatin, which inhibits ACTH secretion in vitro and this is another cause of secondary adrenal insufficiency in malaria [13]. The pituitary contribution had been further corroborated by the observation of depressed thyrotroph and thyroid gland dysfunction in SM [14].

Relative adrenal insufficiency (RAI) has been renamed as "critical illness-related corticosteroid insufficiency" (CIRCI) [4]. Due to limitation of Cosyntropin and Dexamethasone test, random cortisol level below 8.0mg/dl in acute illness is a strong presumptive evidence of RAI or CIRCI [15]. The diagnosis of CIRCI has benefits as it is associated with more frequent use of vasopressors and a worse prognosis in sepsis and SM [4]. Hypoglycemia is frequently recognized as an isolated complication of SM and has been attributed to use of quinine, consumption of glucose by the parasite, cortisol imbalance, hyperinsulinemia [16]. However, with the use of Artesunate in SM, hypoglycemia has been less encountered, and hyperglycemia has been observed in CM and it had been attributed as a factor for high mortality in Kenya [17]. Lactate and alanine are produced from host and parasite are gluconeogenic precursors that enhances gluconeogenesis and hyperglycemia. Insulin secretion is secreted by plasma glucose and potentially inhibited pancreatic beta cell function [18].

Thus, increased plasma insulin with normal glucose indicated insulin resistance, while increased plasma glucose in combination with raised plasma insulin indicates insulin resistance with relative beta cell dysfunction. IR can cause endothelial dysfunction which is an important pathogenetic mechanism of SM. Thyroid hormones play an important role in the adaptation of metabolic functions to stress and critical illness. In SM we found low T3 which can be attributed to increased deiodination of T4 to reverse T3 (rT3) rather than T3 [14]. It is generally accepted that low T3 observed during critical illness constituted part of an adaptive metabolic response, decreasing metabolic function during MODS that help to protect cell survival. It has been observed that thyroid function recovered to normal in majority cases after the critical illness subsides [19]. However, low T3 at the time of admission is a bad prognostic factor. There is depression of thyrotropin and thyroid gland dysfunction causing sick euthyroid syndrome seen in malaria. Further, the inhibitory effect is due to inhibition of TSH release by fever, stress or toxins acting at the level of hypothalamus [14].

Our results showed that in SM and UM there was hypocalcemia with low PTH. This is due to failure of homeostatic mechanism of PTH which is due to parathyroid gland failure. It has been found that recovery of glandular function occurred with the clearance of parasites. This pattern of response is like that of sick euthyroid syndrome and has been described as "sick-euparathyroid" in malaria [20]. The mechanism of hypocalcemia is utilization of calcium by the parasites, acquired calcitriol resistance, 1-α-hydroxylase insufficiency, associated renal failure, and vitamin D deficiency [21]. Hypophosphatemia among patients with SM is another possible explanation of hypocalcemia. Phosphate depletion is associated with hypercalciuria in man [22].

Hypophosphatemia in the present series was more predominant in SM. Hypophosphatemia is associated with hemolytic anemia through reduced erythrocyte deformability, platelet dysfunction and bleeding. Tissue hypoxia and vital organ dysfunction in SM further aggravated by low erythrocyte 2,3-diphosphoglycerate concentration due to hypophosphatemia and low Vit-D has been associated with SM and with mortality [22,23]. Out of these hormones, low cortisol, low T3, low calcium, low Vit-D, and low PTH were associated with high mortality. In sepsis low T3 and low cortisol were associated with increased mortality. Apart

from these hormones increased PCT and inappropriate erythropoietin were also found in critical malaria and SM with anemia [8,9].

However, the clinical features of the endocrine dysfunction in SM are difficult to interpret. Further, the accuracy of laboratory diagnosis has several limitations in relation to circadian rhythm, pharmacokinetic properties of different hormones, and specific requirements of sampling, processing, and storing. Despite these limitations this study showed that multiple endocrine dysfunctions are also a part of complication of SM that require further research.

References

1. World Health Organization, Communicable Diseases Cluster (2000) Severe falciparum malaria. Trans R Soc Trop Med Hyg 94(1): 1-90.

2. Mohapatra MK, Das SP (2009) The Malaria Severity Score: a method for severity assessment and risk prediction of hospital mortality for falciparum malaria in adults. J Asso Physicians India 57: 119-126.

3. Schofield L, Grau GE (2005) Immunological processes in malaria pathogenesis. Nat Rev Immunol 5(9): 722-735.

4. Gheorghita V, Barbu AE, Gheorghiu ML, Caruntu FA (2015) Endocrine dysfunction in sepsis: a beneficial or deleterious host response?. Germs 5(1): 17-25.

5. Muller B (2007) Endocrine aspect of critical illness. Ann Endocrinol 68(4): 290-298.

6. Mohapatra MK, Thomas AG, Bariha PK, Patel DK (2013) Serum procalcitonin as a triage tool for severe Plamodium falciparum malaria. J Trop Dis 1: 123.

7. n.Master version-2.0 (2011) CMC Biostatistics.

8. Matthews DR, Hoskar JP, Rudenski AS, Naylor BA, Treacher DF, et al. (1985) Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentration in man. Diabetologia 28(7): 412-419.

9. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357(3): 266-281.

10. Mohapatra MK, Bariha PK, Mohapatra A (2019) Adrenal insufficiency in severe falciparum malaria: Its outcome and prediction by Discriminant Score. Int J Contemporary Med Res 6(9): 148-155.

11. World Health Organization (2015) Guidelines for the treatment of Malaria, 3rd (Edn.), pp: 1-62.

12. Davis TM, Li TA, Binh TQ, Robertson K, Dyer JR, et al. (1997) The hypothalamic-Pituitary-Adrenal axis in severe falciparum malaria: Effects of cytokines. J Clin Endocrinol Metab 82(9): 3092-3098.

13. Pan JX, Mikkelsen RB, Wallach DF, Asher CR (1978) Synthesis of a somatostatin like peptide by plasmodium falciparum. Mol Biochem Parasitol 25(1): 107-111.

14. Davis TM, Supanaranond W, Pukrittayakamee S, Krishna S, Hart GR, et al. (1990) The pituitary-thyroid axis in severe falciparum malaria: evidence for depressed thyrotroph and thyroid gland function. Trans R soc Trop Med Hyg 84(3): 330-335.

15. Macia BC, Begona POM, Pilar PCM, Asuncion ARM, Castono FG, et al. (2001) Serum cortisol concentration in acute non-critical ill patients, measured in three periods of the day. Med Clin (Barc) 117(1): 254-256.

16. Davis TM, Looareesuwan S, Pukrittayakamaee S, Levy JC, Nagachinta B, et al. (1993) Glucose turnover in severe falciparum malaria. Metabolism 42(3): 334-340.

17. Phillips RE, Looareesuwan S, Molyneux ME, Hatz C, Warrel DA (1989) Hypoglycemia and counter regulatory hormone responses in severe falciparum malaria: treatment with Sandostatin. Q J Med 86(4): 233-240.

18. Eltahir EM, El Ghazil G, A Elgadir TME, A Elbasit IE, Elbashir MI, et al. (2010) Raised plasma insulin level and homeostasis model assessment (HOMA) score in cerebral malaria: evidence for insulin resistance and marker of virulence. Acta Bio Pol 57(4): 513-520.

19. Gutch M, Kumar S, Gupta KK (2018) Prognostic value of thyroid profile in critical care condition. India J Endocrinol Metab 22(3): 387-391.

20. Davis TM, Pukrittayakamee S, Woodhead JS, Holloway P, Chaivisuth B, et al. (1991) Calcium and phosphate metabolism in acute falciparum malaria. Clin Sci 81(3): 297-304.

21. Marcos LG, Andrew PT, Pozzan T, Celia RSG (2003) Calcium signaling in a low calcium environment, how the intracellular malaria parasite solves the problem. J Cell Biol 161(1): 103-110.

22. Davis TM, Singh B, Choo KE, Ibrahim J, Sulaiman SA, et al. (1998) Dynamic assessment of parathyroid function in acute malaria. J Int Med 243(5): 349-354.

23. Bivona G, Agnello L, Sasso BL, Scazzone C, Butera D, et al. (2019) Vitamin D in malaria: more hypothesis than clues. Heliyon 5(2): e01183.