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Review Article

Does Hyperuricemia in Falciparum Malaria Infected Children Explains the Etiology of Burkitt's Lymphoma?

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Abstract: Falciparum malaria still represents the big obstacle to communities in Sub-Sahara African countries and more concentrated efforts against COVID-19 pandemic, may influence the lives of millions of children in that malaria-endemic area. Hyperuricemia associated with plasmodium falciparum infection reflects the density of parasitemia and it may lead to kidney injury, resulting in low vitamin D production. Furthermore, hyperuricemia leads to high levels of proinflammatory cytokines counting interferon γ-induced protein, which is invested vitamin D deficiency in the development of Burkitt's lymphoma. Experimental research is required.

Keywords: Hyperuricemia, Plasmodium falciparum, Vitamin D deficiency, C-MYC gene, Burkitt's Lymphoma.

INTRODUCTION

Burkitt's lymphoma (BL) is the most frequent childhood tumor originate in the tropics and subtropics. It was first recognized by Dr. Dennis Burkitt, a British surgeon, as he was working in Uganda. Burkitt's lymphoma represents for > 60% of childhood tumors in most regions of tropical Africa.

It is a prototype of high grade non-Hodgkin lymphoma characterized by high tumor burden. It is delicately chemo-sensitive, and responds well to treatment. Fast cell lysis leads to release of massive quantities of breakdown products giving rise to the so named "tumor lysis syndrome" with acute renal failure (ARF).

Acute tumor lysis syndrome (ATLS) describes the metabolic derangements that may follow the initiation of cytotoxic therapy and rapid destruction of tumor cells. It may also occur spontaneously when the tumor outgrows its blood supply, leading to ischemia, necrosis, and release of cellular contents such as hypoxanthine, xanthine and uric acid, into the extracellular space. These metabolites can overwhelm the body's normal homeostatic mechanisms and form urinary crystals and precipitates that cause ARF [1]. Serum uric acid in very high concentrations may trigger inflammatory stress, and it may also have intracellular pro-oxidative activity [2].

Study done by Lopera-Mesa TM *et al*., [3] suggested that elevated UA levels may contribute to the pathogenesis of *P. falciparum* malaria by activating immune cells to produce inflammatory cytokines, their association with parasite density and creatinine levels suggest that parasite-derived UA and renal function may be involved.

Inflammatory cytokines produced in the local inflammatory site are capable of promoting the production of reactive oxygen and nitrogen species that in turn damage DNA and promote DNA mutations [4].

Study done by Herbert F *et al*., [5] showed that High amounts of IL-17, IP-10, and IL-10 are predictors of multiple organ dysfunction consequences of

falciparum malaria. While Burkitt's lymphoma children and adolescents showed moderately higher levels of IL-6, IL-17A, IL-10 [6], IP-10 play as an antitumor agent that promotes damage in established tumor vasculature and causes tissue necrosis in human Burkitt lymphomas established subcutaneously in athymic mice [7].

IFN-gamma-inducible protein 10 (IP-10, CXCL10), a chemokine released from cells activated with type I and II IFNs and LPS, is a chemo-attractant for stimulated T cells . Expression of IP-10 is seen in numerous Th1-type inflammatory diseases, where it is thought to play a central role in recruiting activated T cells into positions of tissue inflammation [8].

IP-10 synthesis by Ms is provoked by B cell-derived IL-6 and relies on STAT3 phosphorylation. Furthermore, IP-10 amplifies the production of IL-6 by B cells, which sustains the STAT3 signals that lead to PC differentiation [9].

Study done by Pan J *et al*., [10] suggested that STAT3 inhibition was a potent anti-fibrotic strategy in hyperuricemia-related CKD.

Uric acid and xanthine oxidase may contribute to kidney fibrosis mainly by inducing inflammation, endothelial dysfunction, oxidative stress, and activation of the renin-angiotensin system. Besides, hyperuricemia induces alterations in renal hemodynamics via afferent arteriolopathy and contributes to the onset and progression of kidney fibrosis [11]. And we suggest that lead to vitamin D deficiency.

Study done by Isnuwardana R *et al*., [12] showed that vitamin D deficiency is associated with hyperuricemia , while increasing serum uric acid might be associated with increasing 25(OH)D level.

The pooled prevalence of vitamin D deficiency in Africa was 18-46%, Mean serum 25(OH)D concentrations were lower in populations living in northern African countries or South Africa compared with sub-Saharan Africa, in urban areas compared with rural areas, in women compared with men, and in newborn babies compared with their mothers [13]. Study done by Mogire RM [14] , showed that Approximately 0.6% and 7.8% of young African children were vitamin D deficient as defined by 25(OH)D levels < 30 nmol/L and < 50 nmol/L, respectively.

Study done by Cusick SE [15], found that vitamin D insufficiency is common in Ugandan children, that children with severe malaria have significantly lower levels of 25(OH)D than healthy community children, and that lower levels of vitamin D are associated with increased odds of severe malaria.

Researchers found that B-cell lymphoma patients with deficient vitamin D levels had a 1.5-fold greater risk of disease progression and a twofold greater risk of dying, compared to patients with optimal vitamin D levels after accounting for other patient factors associated with worse outcomes [16].

Study done by Komolmit P [17], showed that upon correction of vitamin D insufficiency or deficiency, the serum IP-10 and DPP IV levels were decreased.

Study done by Hickson MR [18], showed that acute kidney injury was present in 33.2% of children with cerebral malaria and severe malaria anemia.

Vitamin D signaling can suppress expression of genes regulated by c-MYC, a transcription factor that controls epidermal differentiation and cell proliferation and whose activity is frequently elevated in cancer [19].

DISCUSSION

We suggest that hyperuricemia promotes inflammatory response among falciparum malaria infected children, and causes kidney injury which leads to vitamin D deficiency. And raised IP-10 accompanied with vitamin D deficiency leads to the over expression of c-myc gene [20], resulting in Burkitt's lymphoma.

As IP-10 and its receptor, CXCR3, seem to participate to the pathogenesis of several organ specific, or systemic autoimmune diseases [21], and augmented expression of IP-10 and its equivalent receptor CXCR3 have also been related with advanced human cancers, counting B-cell lymphoma [22]. Both of the above-mentioned information support our suggestion.

CONCLUSION

We conclude that falciparum malaria associated Burkitt's lymphoma, induced by hyperuricemia resulting from rupture of erythrocytic schizonts in capillaries of visceral organs, cause renal injury, consequences of the low vitamin D synthesis, dysregulation of the immune system and due to high level of IP-10 and its receptor and over expression of c-myc genes.

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