EDITORIAL

Vivax Malaria: Benign No More

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Malaria still remains an important cause of multisystem organ failure (MSOF) needing ICU care in tropical and developing countries. The 2016 global estimate of malaria was 216 million cases.[1] Ninety percent of these were recorded in WHO African region followed by 7% and 1% respectively in South-East and Eastern Mediterranean regions. A 18% global reduction in malaria incidence is documented; the figures being 76/1000 population in 2010 and 63/1000 in 2016. The Indian data on malaria compiled by National Vector Borne Disease Control Programme (NVBDCP) showed 1.09 million cases in 2016 and 0.67 million cases in 2017 (till September). The incidence of falciparum malaria was 65.53 and 65.32 percent respectively in 2016 and 2017.[2] The 2017 World Malaria Report revealed a high percentage of vivax malaria in WHO regions of the Americas, South-East Asia and Eastern Mediterranean (64, >30 and 40 percent respectively). The global deaths still remain high despite advent of artemisinin based combination therapy (ACT); the figures being 4.46 and 4.45 lakhs in 2015 and 2016 respectively.[1]

Emergence of Vivax Malaria

Saravu.et.al. in a study of 922 patients of malaria in Manipal, Karnataka (2014) showed plasmodium vivax as predominant species (63.4%) vs plasmodium falciparum (34.4%) with mortality of 0.34% and 2.21% respectively. The predictors of mortality were acute respiratory distress syndrome (ARDS) in vivax malaria and MSOF in falciparum malaria.[3] A study of 50 pediatric plasmodium vivax malaria patients from Mumbai by Kumari M and Ghildiyal R (2014) showed 20% needing ICU care with 4% mortality.[4]

Vivax is now reported with increasing prevalence even in Africa. A recent 2016 Ethiopian study by Geleta G and Ketema T in 263 children with malaria showed a complication rate of 23% (46/200) for falciparum malaria. The corresponding figures for vivax and mixed malaria were 31% (9/29) and 29.4% (10/34) respectively.[5]

Malaria - Disease of Complications

These include cerebral malaria, normocytic anemia, hypoglycaemia, metabolic acidosis, acute renal failure and fluid disturbances. Acute pulmonary edema/ARDS, septicaemia with algid malaria and coagulation abvnormalities contribute to morbidity and mortality.

The clinical indicators of poor prognosis are deep coma, convulsions, papilledema, decerebrate/decorticate rigidity or opisthotonus, circulatory collapse, renal failure, ARDS and metabolic acidosis. The laboratory indicators are hyperparasitaemia (>5%), peripheral schizontaemia, PCV <15%, haemoglobin<5gm/dl, RBS <40 mg/dl, BUN >60 mg/dl, creatinine >3 mg/dl, SGOT,SGPT>120 IU/L and high venous lactate >5 mmol/l.[6]

The complications in vivax malaria were outlined in a study of 102 severe plasmodium vivax malaria patients by Patil.et.al (2015). They showed MSOF rate of 43.1% with high rates of haemotological, renal and hepatic dysfunction (89.2, 34.3 and 21.6 percent respectively). The comparative rates of cerebral malaria and ARDS were much lower (7.8 and 2 percent). The mortality rate was 6.9%.[7]

In a study of 539 adult severe malaria patients by Kochar.et.al (2014), 40.26% had MSOF. The risk was greatest with mixed malaria [90.9%,(40/44)], followed by 37.6%, (103/274) and 33.5%, (74/221) respectively for falciparum and vivax monoinfection.[8]

In this issue of journal Trivedi et.al have discussed malaria in Intensive care focusing on patients requiring ICU admission.[9] They have enrolled 100 adult confirmed malaria (70 P.Vivax, 18 P.Falciparum and 12 mixed) patients requiring ICU admission and having SOFA score of 4 or above. Mortality was 21% which was more in vivax (16/70, 22.9%) and mixed (4/12, 33.3%) compared to falciparum (1/18, 5.6%). Mean pulse, respiratory rate, PT-INR and SOFA score was higher and mean BP, GCS, HCO3 and Pao2/Fio2 ratio was significantly lower in expired patients. Respiratory involvement (ARDS) was more in vivax, whereas renal involvement and coagulation derangement was common in falciparum/mixed malaria patients. ARDS, hypotension, lower GCS score, metabolic acidosis and high SOFA score were predictors of mortality.[9]

This study highlights the emerging role of vivax in causing complicated malaria needing intensive care in India. Permanent neurological, hepatic or renal sequelae were not seen in survivors. 10% of survivors of pediatric complicated malaria have neurological sequelae in form of cerebellar ataxia, hemiparesis, speech disorders, hypotonia or spasticity. The use of SOFA score in critically ill malaria patients was validated in this study. The only limitation of the study was admission bias in favor of malaria with ARDS for ventilator support. Due to resource restricted setting of a tertiary referral centre, all complicated malaria patients could not be admitted in the MICU.

Around 50 million women are estimated to be exposed to the risk of malaria in pregnancy annually[10] especially in 1st and 2nd trimester. The ability of infested erythrocytes to sequester in placenta leads to placental malaria with high infant morbidity and mortality.[11] None of the 32 female patients in this study were pregnant.

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Has Advent of Artesunate Improved the Morbidity and Mortality of Malaria?

If 2 drugs with different mode of action and pattern of resistance are used, the pre-parasite probability of developing resistance to both drugs is the product of their individual per-parasite probabilities. So if pre-parasite probability of developing resistance to artemisinin and mefloquine or lumefantrine is 1 in 10,[12] then probability of spontenous resistance with Artemisinin based combination therapy (ACT) would be every 1 in 10^{24}/parasite. The estimated number of malarial parasites in world is 10.[20] This makes resistance to ACT's virtually impossible - once in 10,000 years!!.[12]

Complications in malaria however have not reduced to a significant extent despite ACT. Some of possible reasons are:-

1. Incomplete coverage: Patients receive antimalarial monotherapy instead of ACT.
2. Substandard drugs.
3. Incomplete and inadequate adherence to antimalarial regimen especially in hyperparasitemic patients; vomiting may be contributory.
4. Treatment may be started late. Delay of even 48hours can produce a strong proinflammatory cytokine storm leading to NO induced endothelial damage.
5. Once Systemic Inflammatory Response Syndrome (SIRS) occurs, it may increase despite ACT.

Trivedi et al's article outlined the mechanisms of organ dysfunction in complicated malaria and also the possible reasons for changing clinical profile of vivax malaria. The pharmacological hallmark of artemisinin derivatives is a rapid clearance of parasitaemia (24-48 hours). Does this provoke an intense cytokine storm? ARDS has been noticed to occur even during or after clearance of parasitaemia. Animal studies of anti-inflammatory and immunomodulatory effects of artemisinin derivatives allay this fear.[13]

ARDS and MOSF-Genetic Predisposition and Biomarkers

Genetic susceptibility plays a key role in ARDS pathogenesis especially genes encoding Angiotensin Converting Enzyme(ACE), Interleukin-10, Tumor Necrosis Factor-α (TNF) and Vascular Endothelial Growth Factor (VEGF).[14] ACE has been associated with overall susceptibility to ARDS and the ACE-2 protein is the receptor for the Severe acute respiratory syndrome (SARS) coronovirus. Experimentally induced lung injury from SARS CoV can be attenuated by blocking the RAAS pathway.[14] Similar sites may exist for malaria antigen. Some persons may have multiple genetic variants that modify the risk and outcome of ARDS and MOSF after exposure to infections like malaria, leptospirosis and dengue. This may explain the occurrence of malaria complications in the destined few.

Increased levels of biomarkers like IL-6, angiopoietin 2 have been associated with adverse outcomes in ARDS and these may be under genetic control.[14] The success of human mesenchymal stem cells in ex vivo human lungs injured with live bacteria opens exciting avenues for future treatment of ARDS due to tropical infections.[15]

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