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Antimalarial drug resistance malaria parasite: A review in NE states of India

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ABSTRACT

The eight Northeastern (NE) states sharing a significant proportion of malaria cases reported in every year from India. Nowadays, several classes of antimalarial drugs like chloroquine, sulphadoxine-pyrimethamine, combination drugs artemisinin plus sulphadoxine-pyrimethamine etc. are used for treatment of malaria cases. In NE states, several research works are going on at molecular level for evaluation of new and effective antimalarial drugs. However, the major malaria parasite (P. falciparum) circulating in NE states has developed resistance to all the currently used antimalarial except recently introduced artemether–lumefantrine combination. Keeping in mind, the review study aims to highlight the current research works related to the scenario of antimalarial drug resistance P. falciparum parasite circulating in NE states, distribution of haplotypes and their diversity, vector incrimination etc.

Key words: Antimalarial, Chloroquine, *P. falciparum*, NE, Sulphadoxine-pyrimethamine.

INTRODUCTION

Though, India has now achieved from pre-elimination to control phase of malaria [1], however, there are still some regions where malaria is endemic from time to time. As per national vector borne disease control programme (NVBDCP) report 2014, the state of Odisha (36.27%) and Chhattisgarh (11.44%) shared a major proportion of total malaria cases reported so far from India[2]. The Northeastern (NE) states of India also sharing a large proportion (12% in 2014) of malaria cases every year [2]. The epidemiological data indicated that malaria incidence was highest during June-July and lowest during the month of November in every year [3]. The epidemiology of malaria is quite unique in NE states. There are several reasons like vast geographical diversity, multi ethnicity, parasitic adaptation etc. For treatment of malaria cases, several classes of antimalarial drugs are available in market. But, at the same time, the major malaria parasite *P. falciparum* has developed resistance to most of the commonly used antimalarial drugs so far introduced in public health programme. It throws a huge glow on malaria control strategies. The era of malaria research in India begins from 1897. Since then lots of studies have been carried out on malarial epidemiology, disease transmission, vector incrimination, antimalarial drug resistance, genetic polymorphisms on target parasite enzyme, mutational frequency, circulating haplotypes and their diversity etc. Such studies have provided valuable information which is helpful in controlling malaria incidence upto a huge extent.

Research on antimalarial drug resistance in NE states:

In 1973, the first case of chloroquine (CQ) resistance malaria parasite was reported from Karbi Anglong district of Assam [4-6]. At that time, the CQ has been replaced with sulphadoxine-pyrimethamine (SP) by Govt. of India. In 1979, again SP resistance malaria parasite was detected from Karbi Anglong district of Assam [7]. However during that period, the SP resistance malaria parasite was not reported from other district of Assam. In 1983-1984, Borkakoty BN *et al*., conducted a research work in Assam. The study aimed to perceive the treatment efficacy of *P. falciparum* cases with SP alone or with quinine sulphate. Their finding has shown that SP along with quinine

treatment showed 100% cure rate in all study areas except Karbi Anglong district [8]. However, within few years, the SP resistance malaria was spreading throughout the NE states.

In 2005, Govt. of India has introduced the combination of AS+SP under National Drug Policy for malaria in selected areas where CQ resistance levels was found very high (http://www.nvbdcp.gov.in). However, due to the progressive increase in numbers of SP resistance malaria cases, the combination drug AS+SP was introduced in all malaria repotting states of India during 2010 (WHO,2014). At present situation, several research studies are going on to find out the drug target mechanism and structural conformation of target enzyme as well as binding behavior of antimalarial drugs. Lots of studies have proved that single nucleotide polymorphisms (SNP) at different positions in target enzymes of *P. falciparum* are associated with antimalarial resistance.

Nowadays, large numbers of CQ resistance malaria parasites were reported from Assam. In 1995, Gogoi SC *et al*., studied on the *in vivo* susceptibility of *P. falciparum* to CQ in tea garden tribes of Assam. Their study revealed that 85% cases were S/RI, 7% were RI, 3% were RII and 5% were RIII to CQ [9]. At that time, amodiaquine was used by the clinicians instead of CQ. However, further studies confirmed that the amodiaquine has no advantage in the treatment of patients with CQ resistance *P. falciparum* infection [10]. In molecular level study, C72S, M74I, N75E and K76T mutations in *P. falciparum chloroquine resistance transporter* (*Pfcrt*) gene are established marker for CQ resistance [11-12]. However, still it is debatable. Few studies have shown that the presence of mutations in *Pfcrt* K76T and *P. falciparum multidrug resistance* (*Pfmdr1*) N86Y genes is not sufficient to explain the therapeutic efficacy of CQ to *P. falciparum* [13]. In opposition to this, few results strongly indicated that *Pfmdr1*-N86Y and *Pfcrt*-K76T mutations can be used as molecular markers to identify CQ resistance in *P. falciparum* [14]. Recently, *Pfcrt*–K76T mutation was also observed in *An. minimus* mosquitoes of Assam which was already incriminated as a major malaria vector species of NE states [15-18]. In 2015, a study was conducted by Sharma J *et al*., for detection of mutational prevalence of *Pfcrt* gene among *P. falciparum* isolates in Assam (Karbi Anglong and Tinsukia) and Arunachal Pradesh (Lohit and Changlang district). Their study revealed that K76T mutation was prevalent in 77.78% cases followed by M74I (61.11%), N75E (61.11%) and C72S (16.67%) cases. Triple mutant allele M74I+N75E+K76T was found in 61.11% cases (unpublished data). The study confirmed that *Pfcrt* mutation is still prevalent in NE states.

It has been proved that, there are certain point mutations in dihydrofolate reductase (*dhfr*) and dihydropteroate synthetase (*dhps*) enzymes of SP resistance malaria parasites [19-24]. In 2004, Ahmed A *et al*., studied on prevalence of mutations associated with SP resistance [4,19-21]. They have studied on 312 *P. falciparum* field isolates collected from Assam (only Kamrup district), UP, Orissa, Delhi and Goa. Out of the study areas, maximum 7 *dhfr* genotypes and 15 *dhps* genotypes were detected from Assam [19-21]. According to the study, triple mutant allele A**IRN**I and **AGE**AA genotype was predominant in Assam [19-21]. Their study revealed that a total of 24 *dhfr-dhps* two locus genotypes were reported from Assam of which 70% isolates were having more than four mutations in *dhfr-dhps* gene sequence [19-21]. However at that time, the study was carried out only in Kamrup district of Assam. Hence, the study was not able to explain the mutational prevalence of SP resistance *P. falciparum* malaria parasites circulating in other malaria endemic district of Assam. Recently in 2014, a study was carried out by Sharma J *et al*., in 10 malaria endemic district of Assam and two districts in Arunachal Pradesh [22-24]. They have also found similar finding as earlier reported by Ahmed A *et al*. During the study, 3 *dhfr* haplotypes, 7 *dhps* haplotypes and 9 *dhfr-dhps* two locus haplotypes were observed among the *P. falciparum* isolates of Assam [22]. On the contrary, 4 *dhfr*, 4 *dhps* and 8 *dhfr-dhps* two locus genotypes were detected from Arunachal Pradesh [23]. However few novel findings were also established during the study. Quintuple (more than four mutations in *dhfr-dhps* gene) mutant *dhfr-dhps* allele was reported form Changlang district (upto seven mutations) of Arunachal Pradesh and Chirang district (upto six mutations) of Assam [22-23]. Recently, few studies have shown that not only *P. falciparum*, the *P. vivax* malaria parasites circulating in NE states have also shown increase in frequency of quadruple mutant *dhfr* genotype, however the mutation frequency in *dhps* gene was found very low among the *P. vivax* isolates of NE states [25]. In 2014, another study was carried out by Mohapatra PK *et al*., in 2 districts (Lakhimpur and Hailakandi) of Assam for therapeutic assessment of CQ and SP and assessment of point mutations in concerned gene [26]. Out of 210 *P. falciparum* positive samples, CQ treatment failure was recorded in 69.55% cases and 12.6% cases had shown SP treatment failure [26]. Their study reported that, 99.0% isolates had K76T mutation, 68% with mutant *Pfmdr*-1 genotype (86Y) and all the study cases had S108N+A437G mutation in *dhfr+dhps* gene [26].

In *PfATPase6* gene, mutations at codons L263E and S769N are associated artemisinin resistance [27-30]. These mutant *P. falciparum* isolates were reported from French Guiana and Senegal [28-30]. Till now, such mutant *P. falciparum* isolates are not reported from any part of India[27]. However, reduced *in vivo* susceptibility to artemisinin has been reported from few states of India [27, 31]. Novel *PfATPase6* gene mutation at codon S616F was reported from Changlang district of Arunachal Pradesh [32]. However, further evidence regarding this mutation is not available from any part of the world, whether this mutation is associated with artemisinin resistance or not. Recently, Artemisinin resistance malaria parasite has been reported form Myanmar having K13-propeller mutations [33].

From the above reviews, it is clear that the *P. falciparum* malaria parasites circulating in NE states had shown mutations in *Pfcrt*, *Pfdhr* and *Pfdhps* gene associated with antimalarial resistance. Recently, *PfATPase6* gene mutation was also reported from India [27, 32], however the authors could not correlate such finding with *in vivo* as well as *in vitro* studies. Recently in 2013, Govt. of India has introduced artemether-lumefantrine combination in NE states. Based upon the previous report of antimalarial resistance, the artemether-lumefantrine resistance *P. falciparum* isolates may also occur in near future. So, development of new antimalarial drug is necessary in this region. Recently few scientists has found that the "ferroquine" (derivative of chloroquine) have promising potential antimalarial properties [34]. According to few researchers, dehydroabietylamine and its N-trifluoroacetyl, N-tribromoacetyl, N-benzoyl, and N-benzyl derivatives have also shown excellent activity against *P. falciparum* parasites [35]. The N-dehydroabietylbenzamide showed potent antimalarial activity and at the same time abietane diterpenoids has shown less antimalarial activity [35]. Traditional medicinal plant is also useful for malaria treatment [36]. The Aqueous root extract of Berberis aristata has also shown *in vitro* antiplasmodial activity [37]. Beside this, so many studies are going on in different parts of India as well as in other countries for development of new and effective antimalarial drugs.

CONCLUSION

Further in depth analysis on such antimalarial drugs are necessary for taking advance precaution against the occurrence of artemether-lumefantrine resistance *P. falciparum* isolates in near future.

REFERENCES

[1] WHO. World Malaria report 2014.World Health Organization 2014; 1-227. Available at: http://www.who.int/malaria/publications/world_malaria_report_2014/report/en/index.html
[2] NVBDCP. National vector borne disease control programme. Malaria situation in India. http://www.nvbdcp.gov.in/Doc/mal_situation_June2015.pdf [Last accessed on 10-08-2015]
[3] Dhiman S, Goswami D, Rabha B, Gopalakrishnan R, Baruah I, Singh L, *Southeast Asian J Trop Med Public Health*, **2010**,41,1279-89.
[4] Mullick S, Das S, Guha SK, Bra DK, Sengupta S, Roy D, *et al*., *Trop Med Int health*, **2011**, 16,929-35.
[5] Sharma VP, *Parassitologia*, **1999**, 41,349-53.
[6] Sehgal PN, Sharma, MID, Sharma Sl, Gopal S, *J Com Dis*, **1973**, 5, 175–80.
[7] Das S, Barkakaty BN, Roy JR, *Indian J Malariol*, **1981**, 18, 109–16.
[8] Barkakaty BN, Chakravorty NK, Narasimham MV, *Indian J Med Res*, **1996**, 104,284-7.
[9] Gogoi SC, Dev V, Choudhury B, Phookan S, *Southeast Asian J Trop Med Public Health*, **1995**, 26,228-30.
[10] Misra SP, Nandi J, Lal S, *Indian J Med Res*, **1995**, 102, 119-23.
[11] Ghanchi NK, Ursing J, Beg MA, Veiga MI, Jafri S, Mårtensson A, *Malar J*, **2011**, 10:18
[12] Vinayak S, Biswas S, Dev V, Kumar A, Ansari MA, Sharma YD, *Acta Trop*, **2003**, 87,287–93.
[13] Goswami D, Dhiman S, Rabha B, Kumar D, Baruah I, Sharma DK, Veer V, *J Infect Dev Ctries*, **2014**, 11,768-73.
[14] Shrivastava SK, Gupta RK, Mahanta J, Dubey ML, *PLoS One*, **2014**, 9:e103848.
[15] Sarma DK, Mohapatra PK, Bhattacharyya DR, Mahanta J, Prakash A, *Trop Biomed*, **2014**, 31,557-61.
[16] Dhiman S, Goswami D, Rabha B, Gopalakrishnan R, Baruah I, Singh L, *Southeast Asian J Trop Med Public Health*, **2010**, 41,1279-89.
[17] Dutta P, Bhattacharyya DR, *J Commun Dis*, **1990**, 22, 92-7.
[18] Dev V, Ansari MA, Hira CR, Barman K, *Indian J Malariol*, **2001**, 38, 32-8.
[19] Ahmed A, Bararia D, Vinayak S, Yameen M, Biswas S, Dev V, *et al*., *Antimicrobial Agents and Chemother*, **2004**, 48,879-89.

[20] Ahmed A, Das MK, Dev V, Saifi MA, Wajihullah, Sharma YD, *Antimicrobial Agents and Chemother*, **2006**,50, 1546-49.
[21] Ahmed A, Lumb V, Das MK, Dev V, Wajihullah, Sharma YD, *Antimicrobial Agents and Chemother*, **2006**, 50, 3934-8.
[22] Sharma J, Dutta P, Khan SA, Soni M, Dey D & Mahanta J, *Journal of Postgraduate Medicine*, **2015**, 61, 9-14.
[23] Sharma J, Khan SA, Dutta P, & Mahanta J, *Journal of Vector Borne Diseases*, **2015**, 52,116-21.
[24] Sharma J, Dutta P & Khan SA, *Indian Journal of Medical Microbiology*, **2015**, 33, 401-405.
[25] Prajapati SK, Joshi H, Dev V, Dua VK, *Malar J*., **2011**, 10:102
[26] Mohapatra PK, Sarma DK, Prakash A, Bora K, Ahmed MA, Sarma B *et al*., *PLoS One*, **2014**, 9:e105562.
[27] Saha P, Guha SK, Das S, Mullick S, Ganguly S, Biswas A, *et al*., *Antimicrobial Agents Chemother*, **2012**,56(5), 2511–7.
[28] Eckstein-Ludwig U, Webb RJ, Van Goethem ID, East JM, Lee AG, Kimura M, *et al*., *Nature*, **2003**, 424, 957–61.
[29] Uhlemann AC, Cameron A, Eckstein-Ludwig U, Fischbarg J, Iserovich P, Zuniga FA, *et al*., *Nat Struct Mol Biol*, **2005**, 12, 628–9.
[30] Jambou R, Legrand E, Niang M, Khim N, Lim P, Volney B, *Lancet*, **2005**,366 (99501), 1960–3.
[31] Mishra N, Kaitholia K, Srivastava B, Shah NK, Narayan JP, Dev V *et al*., *Malar J*, **2014**, 13:284.
[32] Sharma J, Dutta P, Khan SA, Soni M & Mahanta J, *Journal of Vector Borne Diseases*, **2014**, 51, 282-285.
[33] Tun KM, Imwong M, Lwin KM, Win AA, Hlaing TM, Hlaing T *et al*., *Lancet Infect Dis*, **2015**, 15, 415-21.
[34] Kumar S, Kumari R, Pandey R, *Protoplasma*, **2015**,252,717-53
[35] Sadashiva MP, Gowda R, Wu X, Inamdar GS, Kuzu OF, Rangappa KS, *et al*., *Exp Parasitol*, **2015**, 155,68-73.
[36] Bora U, Sahu A, Saikia AP, Ryakala VK, Goswami P, *Phytother Res*, **2007**, 21, 800-4.
[37] Chandel S, Bagai U, Semwal RB, Semwal DK, *Pharm Biol*, **2015**, 53,1735-40.