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
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/R, 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 *PfK76T* and *P. falciparum* multidrug resistance (*Pfmdr1*) genes N86Y, K108N and N1467R mutations can be used as molecular markers to identify CQ resistance in *P. falciparum* [11-12]. 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 the presence of *PfK76T* 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 (dihfr) 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 A1RNI and AEGAA 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*, *P. vivax* and *P. malariae* 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 from Changlang district (up to seven mutations) of Arunachal Pradesh and Chirang district (up to 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 *Pfmdr1* 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 \textit{P. falciparum} isolates were reported from French Guiana and Senegal [28-30]. Till now, such mutant \textit{P. falciparum} isolates are not reported from any part of India\cite{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 \textit{P. falciparum} malaria parasites circulating in NE states had shown mutations in Pf\textit{crt}, Pf\textit{dhfr} and Pf\textit{dhps} 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 artmether-lumefantrine combination in NE states. Based upon the previous report of antimalarial resistance, the artmether-lumefantrine resistance \textit{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 \textit{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 artmether-lumefantrine resistance \textit{P. falciparum} isolates in near future.

**REFERENCES**