Clinical, haematological and chemotherapeutic profiles of malaria cases in Hospital Kuala Lumpur: a retrospective review

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Abstract

A retrospective study was carried out on 40 parasitologically confirmed malaria cases admitted to Kuala Lumpur Hospital, Malaysia. Twenty-four cases of *P. vivax*, 14 *P. falciparum* and one each for *P. malariae* and mixed infection were identified. Forty-five percent had gametocytes in the blood at admission. Fever associated with chills and rigors was the most common presenting complaint. Malaria was the provisional diagnosis at admission in only 56.1% of the cases. A high proportion of the patients were anaemic and 88.2% had thrombocytopenia and 30% were hypoglycaemic. The degree of anaemia and thrombocytopenia were significantly associated with pre-treatment parasite density ($p=0.004$ and $p=0.029$ respectively). All the patients responded well to the various combinations of antimalarial drugs used for treatment.

Key words: malaria; clinical; anaemia; thrombocytopenia; Malaysia

Introduction

Malaria is still an important public health problem in Malaysia. For the last 5 years (1992-1996) on average 49,300 cases were reported each year, 75% of which were from Sabah. In Peninsular Malaysia, there was a decrease in the number of cases over the last five years from 9,330 cases in 1992 to 5,884 cases in 1996 and most of these cases (70.1%) were reported among the Orang Asli (aborigines). Clinical data on malaria in Malaysia is very limited. Kuala Lumpur Hospital (HKL) is a National Referral Centre with 2,700 beds. Although malaria is endemic in the country, only severe cases or cases imported from endemic areas within and outside the country were referred to HKL. In countries where malaria is non endemic, misdiagnosis is a common problem. In a study by Winters & Murray (1992), no improvement in the accuracy of the diagnosis of malaria was noted over a period of 30 years among general practitioners in New York. In malaria endemic countries, a similar problem occurs, especially in highly specialised government or private hospitals, that cater for the surrounding population. In a review of malaria cases admitted to the Medical Department of Universiti Kebangsaan Malaysia, Moore & Cheong (1995) found that only 63.0% of the cases were correctly diagnosed at admission. They attributed this to the variable clinical presentations and the difficulty in obtaining accurate history from the patients or relatives. However, the commonest presentations were fever (98.8%), chills/sweats (88.9%) and gastrointestinal symptoms (48.1%) in their series. Comparing local and imported cases, they found no significant differences in terms of severity and abnormal haematological parameters. In this retrospective study, our objective was to describe the clinical manifestations, diagnosis, management and haematological profiles of malaria in relation to species and parasitaemia.

Materials and Methods

Case notes of all patients with a discharge diagnosis of malaria admitted ro the government units in HKL from January 1989 to December 1996 were collected and examined. Only confirmed cases with ar least one positive blood slide for malaria parasite were selected. The relevant clinical manifesrations were recorded. Diagnosis made by the first attending doctor in the ward was taken as the provisional diagnosis. The following criteria were used for the purpose of classification and analysis:

Anaemia - Peripheral venous haemoglobin (Hb) level of less than 13gm% for male and 12gm% for female. A level of less than 5gm% was considered as severe anaemia.

Thrombocytopenia - Platelet count of less than $150x10^9$/L. Platelet count of less than $100x10^9$/L was considered as severe thrombocytopenia.

Hypoglycaemia - Random blood sugar (RBS) of less than 5.0 mmol/L.

Prior to 1990, malaria parasite density was reported qualitatively following the plus system (+ - ++++). Thereafter, the parasite density was reported quantitatively as the number of asexual/sexual stages per microlitre of blood. The calculation was standardized for all government hospitals based on the number of white blood cells (WBC) assuming that there were 8,000 WBC per microlitre of blood. Only those cases with parasitaemia

reported quantitatively were used to correlate haemarological and biochemical parameters with parasitaemia.

Dara were entered into a data base. Statistical analysis were carried out using SPSS® programme. The association between parameters were tested using chi-square, Fisher's Exact test, Mann-Whitney U test and Spearman rank correlation coefficient (r_s) test where appropriare.

Results

Patients characteristics

A toral of 48 case notes were traced but only 40 were parasitologically confirmed malaria cases based on blood microscopy results. Out of these cases, 24 (60%) were *Plasmodium vivax*, 14 (35%) were *P. falciparum* and one each *P. malariae* and mixed infection (*P. falciparum* & *P. vivax*). The patients were predominantly male (35 cases) with a mean age of 31.97 years (range: 13-63 years old). The majority of the cases were Malays (n=27, 67.5%), followed by Chinese (n=5, 12.5%), Indians (n=4, 10%) and others (n=4, 10%). Thirty-two infections (80%) were acquired locally while the rest were imported from other countries. A high proportion of the patients (45.5%) already had gametyocytes in the blood at admission. The proportion of patient with falciparum and vivax malaria having gametocytes was 33.3% and 85% respectively (p=0.010).

Clinical manifestations

Three were referred cases, 6 were relapses and the remaining 77.5% of the cases presented acutely for rhe first rime at HKL. Two of the cases referred showed evidence of grade RII/RIII (no complete clearance of asexual parasitaemia) resistance to chloroquine. Fever associated with chills and rigor were the most common presenting problems (65.8%) followed by headache (26.8%), nausea and vomitting (26.8%), myalgia (17.1%), lethargy (7.3% and other manifestarions (7.2%). Only 56.1% percent of the cases (inclusive of the relapsed and referred cases) were provisionally diagnosed as malaria by the first attending docror in the wards. Other provisional diagnoses made were viral fever (19.5%), dengue (7.3%), fever for investigation (4.9%) and others (9.6%).

Haematological parameters

Most of rhe male patients were anaemic (<13gm%) at admission. A higher proportion of rhe anaemic patients were associated with *P. vivax* infection (61.9%) as compared ro 45.4% among *P. falciparum* infection but the difference was not significant (p=0.465). Severe anaemia was also slightly higher in *P. vivax* than *P. falciparum* infection (33.3% and 27.3% respectively, p=0.661). Among anaemic parienrs, the mean Hb level among *P. falciparum* and *P. vivax* were 10.3 ±2.1 gm% and 11.0 ± 1.4 gm% respectively (p=0.588). There was a significant correlation between pre-treatment parasitaemia and Hb level in *P. falciparum* infection (r_s=0.85, p=0.004) but not in *P. vivax* infection (r_s=-0.25, p=0.143).

Out of 34 patients with available platelet counts, 88.2% had thrombocytopenia. The proportion of thrombocytopenia was higher in *P. vivax* infections (91.3%) than in *P. falciparum* infection (81.8%, p=0.579). Severe thrombocytopenia was also slightly higher in *P. vivax* than *P. falciparum* (65.2% and 63.6% respectively, p=0.998). Although rhe platelet count was lower in *P. vivax* infection (85.6 ±42.8x10^9/L) than in *P. falciaprum* infection (100.7 ± 79.2x10^9/L), the difference was nor staristically significant (p=0.473). However, there was a significant correlation between pretreatment parasite density and platelet level in *P. falciparum* infection (r_s=-0.69, p=0.029) but not in *P. vivax* infection (r_s=-0.175, p=0.230).

The mean RBS level was within the normal range in patients with *P. falciparum* and *P. vivax* (6.12 ± 1.08 mmol/L and 7.05 ±2.67 mmol/L respectively, p=0.516). Thirty percent were hypoglycaemic at admission and the proportion of hypoglycaemia in *P. falciparum* and *P. vivax* was 27.3% and 33.3% respectively (p=0.661).

Treatment and responses

For *P. falciparum* infection, 57.1% received combinations of chloroquine and sulfadoxine-pyrimethamine (CHL-SDX/PYR), 35.7% quinine (QUI) and 7.2% other drug combinations as the first line antimalarial treatment. For *P. vivax*, the proportion of parients receiving CHL-SDX/PYR, QUI and other drug combinations was 37.5%, 54.2% and 8.3% respectively. There was no significant difference in parasite clearance rime (PCT) and temperature normalization rime (TNT) between species for the same drug combinations and between drug combinations for the same species (Table 1). Only two cases developed complications. One had acute renal failure with evidence of disseminated intravascular coagulation and the other had pulmonary oedema. Both patients however had full recovery after treatmenr.

Discussion

Malaria is still endemic and an important public health problem in Malaysia with more than 45,000 cases reported each year. However, because of the easy accessibility of good medical services in the peripheral health centres and hospitals in the country and systematic malaria control strategies, only few cases were seen at HKL, the National Referral Centre. This is further reflected by the fact thar only 7.3% of the cases in this review were referred cases. In 1995, the case fatality rate for malaria was only 0.059%, with most dearhs being in Sabah. Nevertheless, despite rhe endemicity of the infection, rhe clinical diagnosis of malaria, especially in

Table 1. Parasite clearance time (PCT) and temperature normalization time (TNT) among *P. falciparum* and *P. vivax* patients treated with different antimalarial drug combinations

Species	Antimalarial Drug	PCT (hrs) (mean ± sd)	TNT (hrs) (mean ± sd)
Plasmodium falciparum	CHL-SDX/PYR	81.00 ± 46.14[a]	205.87 ± 323.39[b]
	QUI	78.00 ± 36.00[c]	72.00 ± 33.94[d]
Plasmodium vivax	CHL-SDX/PYR	58.66 ± 27.12[e]	167.00 ± 314.51[f]
	QUI	153.25 ± 267.68[g]	141.25 ± 272.87[h]

P values: (a) Between species i) PCT, a&e=0.304, c&g=0.802 ii) TNT, b&f=0.289, d&h=0.707; (b) Between drugs i). PCT, a&c=0.931, e&g=0.124 ii). TNT, b&d=0.302, f&h=0.942

modern medical centres appears to be a problem. Although clinical criteria for the diagnosis of malaria is non-specific, fever particularly intermittent fever, chills, rigors and/or sweating are good predictors of the disease (Kwiatkowski & Greenwood, 1989; Gomes *et al.*, 1994). The majority of the cases in this review presented with these classical symptoms, probably because they presented late to the hospital, when the infection had already been established. This late presentation is supported by the fact that 45% of cases already had gametocytes in their blood. Despite the presence of these classical symptoms, malaria was clinically diagnosed in only 56.1% of the cases in this review.

Anaemia and thrombocytopenia are common findings not only in *P. falciparum* and *P. vivax* but also in other human malaria infections. Unlike thrombocytopenia which is considered a consistent feature of uncomplicated malaria, severe anaemia may be fatal. Anaemia is a major complication especially in children with falciparum malaria. In Gambia, 8% of deaths were attributed to anaemia due to malaria and in Kilifi, Kenya, severe anaemia is responsible for more deaths than cerebral malaria (Greenwood *et al.*, 1991; Marsh, 1992). Our rate of thrombocytopenia is consistent with the findings of others (Kueh & Yeo, 1982; Sharma *et al.*, 1992). Unlike anaemia, the pathogenesis of thrombocytopenia in malaria infection remains uncertain. Immunodestruction was earlier postulated but this has been disputed (Looreesuwan *et al.*, 1992; Sen *et al.*, 1994). The clinical significance of this condition is also not clear. The platelet count in uncomplicated *P. falciparum* and *P. vivax* infection was not significantly different from those of severe cerebral malaria patients (Looareesuwan *et al.*, 1992). There appeats to be no significant relationship between thrombocytopenia with disseminated intravascular coagulation in this review and other studies (Vreeken & Cremer-Goote, 1978; Sharma *et al.*, 1992). The significant correlation between pretreatment parasite density and degree of anaemia and thrombocytopenia in *P. falciparum* but not in *P. vivax* infections is probably due to the lower parasite burden in the latter where parasitaemia seldom exceeds 2%. The severity of anaemia and thrombocytopenia is also more pronounced in chronic than acute falcipatum malaria (Sen *et al.*, 1994).

A higher proportion of anaemia and severe anaemia among patients with *P. vivax* observed in this review (although not significantly different from *P. falciparum*) was also observed amongst malaria patients admitted to other hospitals in the city (Sidhu & Ng, 1991). The same observations were also noted for thrombocytopenia and hypoglycaemia. These observations are not consistent with the general impression that *P. falciparum* causes more severe disease than *P. vivax* and that megaloblastosis and other patterns of erythropoiesis is more commonly seen in *P. falciparum* infections (82%) than 26% in *P. vivax* (Sen *et al.*, 1990). Prolonged *P. vivax* infection as reflected by the significantly higher proprotion of patients with gametocytes at admission could probably account for the higher proportion of anaemia and thrombocytopenia seen in this review.

The guidelines on the management of malaria produced by the Ministry of Health Malaysia recommended that CHL ± SDX/PYR be used as the first line treatment of falciparum malaria and CHL alone for vivax malaria, based on the doses recommended by WHO. Primaquine is indicated for all cases of malaria to eradicate the gametocytes and to prevent relapse in *P. vivax* infection. The liberal use of antimalarial drugs particularly quinine in this review is of concern. There appears to be no apparent clear indication for the extensive use of quinine for vivax malaria as vivax resistance has never been reported in the country. On the other hand, CHL and SDX/PYR resistant falciparum malaria is quite widespread with overall resistance rates of 63.6% and 47.4% respectively in Peninsular Malaysia (Hakim *et al.*, 1996). However, resistance was not the indication of quinine usage in these patients as all the patients treated with CHL and SDX/PYR combination responded well to the regimen. The spread and intensification of drug resistance requires reassessment of the objectives of therapy, choice of treatment and the criteria on which therapy is based upon. The objective of therapy should not only aim at complete parasitological clearance but also resolution of clinical manifestations. Steps that need to be taken include the administration

of antimalarial drugs on the basis of a reliable parasitological diagnosis, adequacy of the dosage regimen and the employment of a mechanism to monitor treatment response to detect treatment failures. Proper parasitologically and clinically-indicated dispensing of antimalarial drugs not only help to prevent unnecessary drug pressure that could lead to development of drug resistance but also help to prevent undesirable adverse side-effects, particularly with quinine.

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