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Factors Affecting Delayed Diagnosis of *Plasmodium vivax* Malaria in the Republic of Korea*

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Abstract: Estimation of the time from onset to diagnosis and analyses of characteristic factors was undertaken for vivax malaria cases diagnosed 1999-2003 and residing in non-malarious areas in Korea. Survival and multiple regression analyses revealed that those residing in provinces with major malarious areas and onset during the malaria season were diagnosed significantly earlier. It was considered that the identified factors reflect three important epidemiologic and ecological characteristics of vivax malaria in Korea: Spatially localized transmissions, clear seasonality in population dynamics of the vector and the partly prolonged incubation period.

Key words: *Plasmodium vivax*, malaria, epidemiology, incubation period, Republic of Korea

INTRODUCTION

Following the diagnosis in 1993 of a vivax malaria case without a history of overseas travel (Chai *et al*., 1994), a malaria epidemic caused by *Plasmodium vivax* has lasted for more than 10 years and so far involved more than 20,000 cases in the Republic of Korea (Lee *et al*., 2002). Based on detailed surveillance records, a clear geographic heterogeneity of transmission exists. The epidemic reflects the simultaneous increase of vivax malaria in North Korea (Ree, 2000) and transmissions are mostly localized to the demilitarized zone (DMZ), with more than 70% of the cases among Korean nationals being soldiers or veterans who frequented this area (Park *et al*., 2003). However, vivax malaria cases have also been diagnosed in non-malarious areas among those who visited malarious areas, indicating that the current epidemic is a nationwide threat (Kim, 2001). In this context, it is crucial to ensure Early Diagnosis and Treatment of Malaria (EDTM) to prevent further transmissions in non-malarious areas and to promote effective treatment. This study characterizes the time delay distribution between onset and diagnosis as well as analyses of its epidemiologic determinants in non-malarious areas of Korea from 1999-2003.

MATERIALS AND METHODS

In the Republic of Korea, vivax malaria is a notifiable disease and so must be reported to public health centers and then to the Korea Centers for Disease Control and Prevention (KCDC). We

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analyzed a total of 862 notified cases residing in non-malarious areas that had date of onset (i.e., fever and chills) clarified and a confirmed diagnosis. In addition to these dates that yield our outcome, sex, occupation, prior chemoprophylaxis (using chloroquine and primaquine) and place of residence were also obtained. As already known to be at risk of contracting vivax malaria, Korean soldiers or veterans (working at the DMZ) were examined as an occupational variable and those who lived in two provinces (Gyonggi-do and Gangwon-do), which include major malarious areas (sub-regions called si and gun) adjacent to the DMZ, were investigated as being the place of residence.

We first characterized the statistical distribution of time from onset to diagnosis. Other exposures were measured as dichotomous variables. To examine the relationship between time delay and binary responses, the distribution was stratified by each exposure factor. The stratified time delays were compared using Kaplan Meier survival functions and the log rank statistic. A multiple regression model was used to determine factors contributing to the delayed diagnosis and to eliminate potential confoundings. We selected the set of variables to be included in the model by a stepwise method (with p-values to enter at 0.25 and to leave at 0.10). Statistical significance was set at $\alpha = 0.05$. All statistical data were analyzed using statistical software, JMP IN ver. 5.1 (SAS Institute Inc., Cary, NC).

RESULTS

The mean (and standard deviation, SD) of the time from onset to diagnosis was estimated to be 12.4 (14.1) days. The minimum and maximum delays were 0 and 179 days, respectively. Skewness and kurtosis were 4.27 and 34.43, respectively, indicating the distribution was extremely skewed to the right. Table 1 shows numbers for each selected exposure variable. Reflecting the majority of cases being soldiers or veterans, as described earlier, 95.1% (n = 820) were male. The mean (and standard errors, SE) time delay of male and female cases was 12.3 (0.5) and 13.9 (2.7) days, respectively and the difference was not significant (log-rank $\chi^2_1 = 0.33$, $p = 0.57$). Distributions of time delay also did not significantly differ by occupational status (log-rank $\chi^2_1 = 0.01$, $p = 0.93$ for student or not and log-rank $\chi^2_1 = 0.06$, $p = 0.80$ for prior or present experience of military service). Although it is not difficult to imagine the chemoprophylaxis might have masked certain symptoms, which could delay diagnosis and indeed a case with the maximum time from onset to diagnosis had received chemoprophylaxis, this preventive measure did not influence the difference (log-rank $\chi^2_1 = 0.18$, $p = 0.67$) (Table 1).

The Kaplan Meier survival curves for stratified time from onset to diagnosis by place of residence (province with malarious areas or others) and by time of onset (during malaria season or not) are shown in Fig. 1. The mean (and SE) of the time among those who resided in Gyonggi-do or Gangwon-do (n = 116) and others (n = 746) was 9.6 (0.9) and 12.8 (0.5) days, respectively. People living in the two provinces were diagnosed significantly earlier (log-rank $\chi^2_1 = 7.05$, $p<0.01$). Further, the mean (and SE) of those who developed the disease between May and September (n = 738) and others (n = 124) was 11.6 (0.5) and 17.0 (1.7) days, respectively, demonstrating that the diagnosis for those who developed symptoms during a non-malaria season was significantly delayed (log-rank $\chi^2_1 = 13.0$, $p<0.01$). After controlling the confounding variables using the multiple regression model, the final

Table 1: Selected exposure characteristics among 862 vivax malaria cases with known dates of onset and diagnosis in non-malarious areas in the Republic of Korea from 1999-2003

Characteristics	n	%
Sex = Female	42	4.9
Occupation		
Student	446	51.7
Military service†	659	76.5
Chemoprophylaxis	284	32.9
Place of residence		
Seoul	326	37.8
Incheon	57	6.6
Busan	56	6.5
Gyonggi-do and Gangwon-do	116	13.6
Onset of symptoms in malaria season‡	738	85.6

†Previous or present history of military service, ‡Those developing the disease from May to September

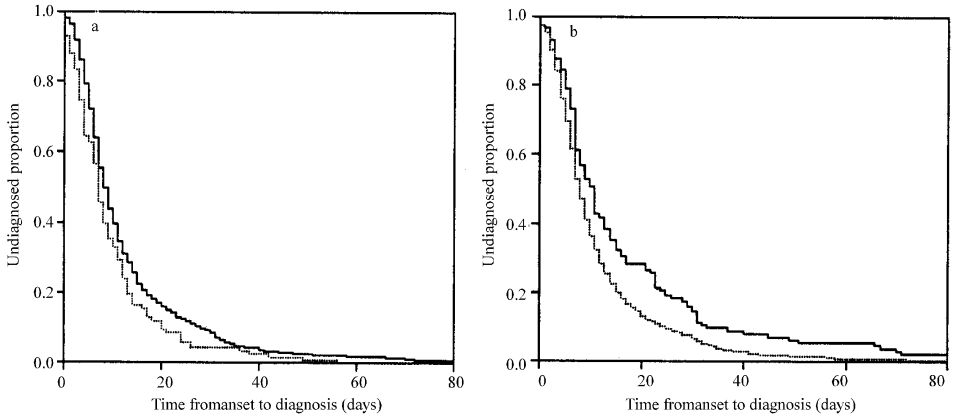

Fig. 1: Kaplan Meier survival functions for time from onset to diagnosis by exposure characteristics, a) By place of residence: those who live in Gyonggi-do or Gangwon-do (thin line) and others (thick line). b) By time of onset: those who developed symptom between October and April (thick line) and between May and September (thin line)

model appeared overall to be a weak model for prediction (adjusted $R^2 = 0.021$, F-ratio = 2.498, p = 0.11). The model identified the two variables as those statistically associated with the time delay: provinces that include malarious sub-regions (Regression coefficient = -1.494, F-ratio = 4.630, p = 0.03) and onset of disease during the malaria season (Regression coefficient = -2.658, F-ratio = 15.495, p<0.001) (Fig. 1).

DISCUSSION

The distribution of time from onset to diagnosis was characterized with clarified determinants based on 862 vivax malaria cases in Korea from 1999-2003. Malaria cases living in the two provinces that include malarious areas were diagnosed earlier and cases that developed the disease in non-malaria season also underwent delayed diagnosis. Previous or present history of military service and prior chemoprophylaxis were not useful predictors of any delayed diagnosis. The identified factors reflect three important epidemiologic and ecological characteristics of vivax malaria in Korea: (1) Transmission is spatially localized around the DMZ (Kho *et al*., 1999; Park *et al*., 2003), (2) the major vector *Anopheles sinensis* shows clear seasonal patterns in its population dynamics and other entomological characteristics (Ree *et al*., 2001; Lee *et al*., 2002) and (3) the incubation period of the Korean strain vivax is likely, in part, to be prolonged (Shute *et al*., 1977; Park *et al*., 2003). Since we observe cases even during the winter season due to the long-term incubation period, obtaining a history of possible exposure in malarious areas among patients with febrile illnesses might have an important role in daily clinical practice.

Present findings imply it is important at least to always keep the potential of contracting malaria in mind even in non-malarious areas and in this way help to prevent further local transmissions of vivax malaria, which in general shows relatively mild symptoms compared to those of *Plasmodium falciparum* infections (Warrell and Gilles, 2002). In addition to previous claims of the importance of EDTM in tropical areas (Tanner and Vlassoff, 1998; Giao *et al*., 2005), our findings suggest the crucial element of early diagnosis to break the chain of malarial transmission in temperate zones. Given the present trends of malaria being imported into temperate countries (Askling *et al*., 2005), our study has important implications in respect of ensuring an early diagnosis, not only for the effectiveness of treatment but also for the prevention of local transmission so that vivax malaria cases such as those can persist in Korea, a temperate zone, do not induce further local transmissions.

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