Patterns of presentation of malaria in a tertiary care institute in Saudi Arabia

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ABSTRACT

Objective: The occurrence of malaria in a non-endemic area is an exceptional event. Review of clinical experience at the King Faisal Specialist Hospital & Research Centre (a tertiary medical centre located in a non-endemic area) demonstrated a relatively frequent infection rate among patients. We therefore examined circumstances that could contribute to the high rate of occurrence observed.

Methods: We retrieved archived blood smears of patients diagnosed with malaria from the records of the Hematology Section of King Faisal Specialist Hospital & Research Centre, Riyadh, Kingdom of Saudi Arabia, followed by a review of the clinical records to extract demographic data, clinical presentations including history of proximate blood transfusion, and travel to, or residence in, areas endemic for malaria.

Results: There were 217 patients diagnosed with malaria between 1978 and 1999, (1398 to 1419 Hejira calendar) resulting in an average yearly frequency of 9.86 cases. Males were 2.6 times more frequently affected than females ($p<0.001$). The majority of patients were infected through natural means, either by residence in endemic areas (N=83) or by travel to one (N=90). A significant minority, 44 (20.3%), became infected through blood transfusion. The majority of blood transfusion-induced malaria occurred in patients who were immunocompromised for various reasons, mostly related to dysfunction of the hematopoietic system or to major surgical insult. The most frequently implicated organism was *Plasmodium falciparum*, accounting for 74.2% of cases, whilst *Plasmodium vivax* accounted for 25.4%.

Conclusion: We demonstrate that patients presenting with malaria are more likely to be males who have been exposed during travel to endemic areas or through blood transfusion. In all cases, *Plasmodium falciparum* is the most likely organism to be implicated.

Keywords: Malaria, blood transfusion, risk factors, immune dysfunction.

Saudi Med J 2002; Vol. 23 (5): 562-567

Malaria is a serious, often fatal infection causing 1.5 to 2.7 million deaths annually worldwide.[1] The infection is caused by the plasmodium parasite of which there are 4 species affecting humans. In the natural state, transmission is through the bite of the blood-sucking anopheles mosquito. The disease used to be endemic in many parts of the non-tropical world as well as in sub-tropical and tropical regions, but is now largely confined to the latter. Apart from the natural route of transmission, malaria can also be transmitted through contaminated hypodermic syringes and needles[2] and by blood transfusion (BT), in which all blood components as well as whole blood, have been implicated.[3-12] Transmission through BT, a particularly unfortunate iatrogenic incident, may be largely avoidable in non-endemic areas. Using current guidelines for donor screening, it is possible to reduce this route of transmission significantly, but in endemic and areas adjacent, this route of transmission remains a potentially serious problem. This risk has been previously recognized in the Kingdom of Saudi Arabia (KSA),[13] and in this

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Received 15th June 2001. Accepted for publication in final form 25th December 2001.

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report we examine the possibility that special risk factors may be at play in the development of clinical infection in recipients of blood components carrying parasites.

Methods. We retrieved archived blood smears from the records in the Hematology Section of the Department of Pathology and Laboratory Medicine at the King Faisal Specialist Hospital and Research Centre (KFSHRC), Riyadh, KSA. This was followed by a review of the relevant clinical records of patients whose blood films were positive for malaria parasites. We extracted demographic data, clinical presentations, history of proximate BT, and of travel to, or residence, in areas endemic for malaria. We also retrieved and recorded relevant hematological data. In addition, we extracted from the records of the Blood Transfusion Service, the type and number of units of blood components transfused during the study period as well as the number of donor units collected. We categorized mechanisms of infection into 3 groups: (a) natural or infection acquired by normal domicile in an endemic area; (b) travel acquired, that is, infection acquired when traveling from a non-endemic area through, or to an endemic one; (c) BT acquired, based on an absence of a history of (a) and (b) above, and of receiving BT within 6 months of the clinical infection.

Results. Two hundred and seventeen patients were identified with malaria occurring between January 1978 and December 1999, corresponding approximately to the Hejira (H) years 1398 to 1419. Of these, only 60 (27.6%) were females (**Table 1**). The ages ranged from one month to 61 years (mean, 30 years, median 32 years).

Plasmodium species. *Plasmodium falciparum* (*P.falciparum*) was identified in 152 cases (74.2%) whilst *P. vivax* was found in only 52 cases (25.4%). There was one case of *P. malaria* (**Table 2**) and no case of multiple infections was seen. Twelve cases could not be reliably classified due to scanty parasitemia. The level of parasitemia varied from low (0.01%) to high (4%) infected red blood cells (RBC).

Modes of infections. Since Riyadh, KSA is located in an area non-endemic for malaria, it was relatively easy to identify mechanisms of infection. Using the classification system outlined in the methods section, 83 (38.2%) patients had acquired their infection by natural means, 90 (41.5%) by travel and 44 (20.3%) through BT (**Table 3**). The nationality profiles of the 3 categories of infection are shown in **Tables 1-3**. Ninety-three (42.9%) were Saudis, 63 (29%) were Sudanese, 18 were Yemeni, 16 were of unknown nationality and the rest, other nationalities including Indo-Pakistanis, Europeans and North Americans. Although Saudis dominate in

Table 1 - General demographics of patients with acute malaria.

Nationality	Male	Female	Total
Saudi	61	32	**93**
Sudanese	52	11	**63**
Yemeni	16	2	**18**
Indo-Pakistani	4	7	**11**
North American	3	4	**7**
Others	7	2	**9**
Unknown	14	2	**16**
Total	**157**	**60**	**217**

Table 2 - Species of infecting plasmodia.

Nationality	Falciparum	Virax	Malaria	Undetermined	Total
Saudi	78	8	1	6	**93**
Sudanese	38	21	-	4	**63**
Yemeni	15	3	-	-	**18**
Indo-Pakistani	-	11	-	-	**11**
North American	4	3	-	-	**7**
Others	4	5	-	-	**9**
Unknown	13	1	-	2	**16**
Total	**152**	**52**	**1**	**12**	**217**

Table 3 - Routes of infection and nationalities.

Mode of infection	Saudis	Non-Saudi	Total
Natural	59	34	**83**
Travel	4	86	**90**
Blood Transfusion	3	11	**44**
Total	**93**	**123**	**217**

natural and BT-associated infections, they constitute a significant minority in travel-acquired infections (**Table 3**). **Table 1** also shows the clear male disadvantage in all nationalities and categories of infection. Using the x^2 test, the difference between the number of males and females was highly significant ($x^2 = 21.786$, $p < 0.001$). **Figure 1** shows how the annual numbers of all malaria cases diagnosed have increased progressively between 1398 and 1419H averaging at an annual rate of 9.86 cases per year. There were 44 cases of BT induced malaria (BTIM) resulting in a rate of 2.0 cases per year.

Factors influencing observed frequencies. Three modes of infection had been clearly demonstrated, we investigated correlates that could be determinants contributing to the observed relative frequencies. (1) Number of patients admitted during study period. Firstly, we examined factors that could have influenced the annual increases in cases sustained throughout the 22-year study period. For these, we compared the hospital annual patient discharges as the most obvious factor, reflecting overall clinical activity in the hospital. Using figures for 1410 – 1419H (years for which complete figures were available) we show that the number of cases of malaria moved in parallel with the number of annual discharges (**Table 4**), resulting in a significant correlation coefficient of 0.8365 ($p<0.001$). This relationship suggests that overall malaria infections seen at KFSHRC reflect the hospital's total clinical activity. (2) Rates of blood transfusion. The next factor we considered as a possible determinant for the pattern and number of cases seen, was the rate of blood transfusions in the hospital. For this we used the number of units of red blood cells concentrates (RBCC) transfused, since RBC would be the vehicle most likely to contain the largest number of infecting organisms. Records demonstrate a consistent annual increase in the number of units of these components transfused from 11.6 in 1410H to 15.7 in 1419H (**Table 4**). Relating the yearly numbers of malaria cases to the annual number of RBCC transfused, it was evident that as the number of RBCC transfused increased, so did the number of natural malaria cases diagnosed. Using Pearson's correlation, we obtained a correlation coefficient of 0.5986 with a significant p value of <0.001. Although these rates of increase almost exactly paralleled the number of patient discharges, this link was not apparent when this type of analysis was applied to BTIM (r=-0.0014). (3) Primary or intercurrent diagnosis in patients with malaria. Patients who acquired their infection through mosquito bites typically presented with uncomplicated febrile illnesses, with overall clinical history suggestive of malaria. This was especially the case among those exposed during travel, and who, in general, had no underlying medical disorders. On the other hand, patients who contracted their infection via BT, of necessity had an underlying illness or, had undergone a procedure requiring transfusion. The underlying illnesses and procedures are outlined in **Table 5**. The majority of patients in this category were Saudis (**Table 3**), and had illnesses that could result in immunosuppression. **Table 3** also shows that patients infected in the natural way were predominantly Saudis.

Discussion. We describe the pattern of presentation of a highly selected series of 217 patients with malaria seen in a single institution in an area in KSA that is non-endemic for malaria. Of these, 108 (51.4%) were non-Saudis, the majority of whom (number [n] = 104) acquired their infection through the bite of mosquitoes. Likewise, of the 93 Saudis, representing 46.3% of patients, the majority (63 or 67.7%), acquired their infection through mosquito bites. Thirty-three of the 93 Saudis (35.5%) on the other hand, apparently became infected through BT, a situation that raises significant issues for the medical management of sick patients in the hospital. However, why only some sick patients receiving BT became infected is unclear, since it may be assumed that each infective donation, according to standard blood bank practice, is likely to have been transfused to 3 or more recipients, either as RBCC fractions, platelet concentrates, or plasma products. In effect, it may be expected that when transmission by BT occurred, it would have done so in clusters. No such clusters were recognized, which suggests that either a clinical diagnosis of malaria was missed, or the infection may have been aborted in others. That many of these patients were on antibiotic drugs and anti-tumor chemotherapy agents, could have played a role in preventing clinical infections. Alternatively, BT-induced infection may have been missed due to the setting of an intercurrent illness, the diagnosis may have been obscured. And since many of these patients had serious disease, a fatal outcome could have permanently erased the evidence for malaria. For those patients whose underlying illness did not result in death and who were discharged, outpatient follow up evaluation at KFSHRC should have revealed malaria, if present, as was indeed the case in some. And for those followed elsewhere, it is possible that some may have been diagnosed with malaria and treated without recognition that the infection might have been iatrogenically acquired. This last scenario is unlikely, however. First, due to local epidemiology and, secondly, because of the requirement that all cases of malaria be reported to the Public Health authorities. All such cases should therefore have been eventually traced back to this hospital. Thus, although we have almost certainly not detected all patients who could have become infected through transfusion, we recognize a total of 44 patients (33 Saudis), perhaps the majority, acquiring

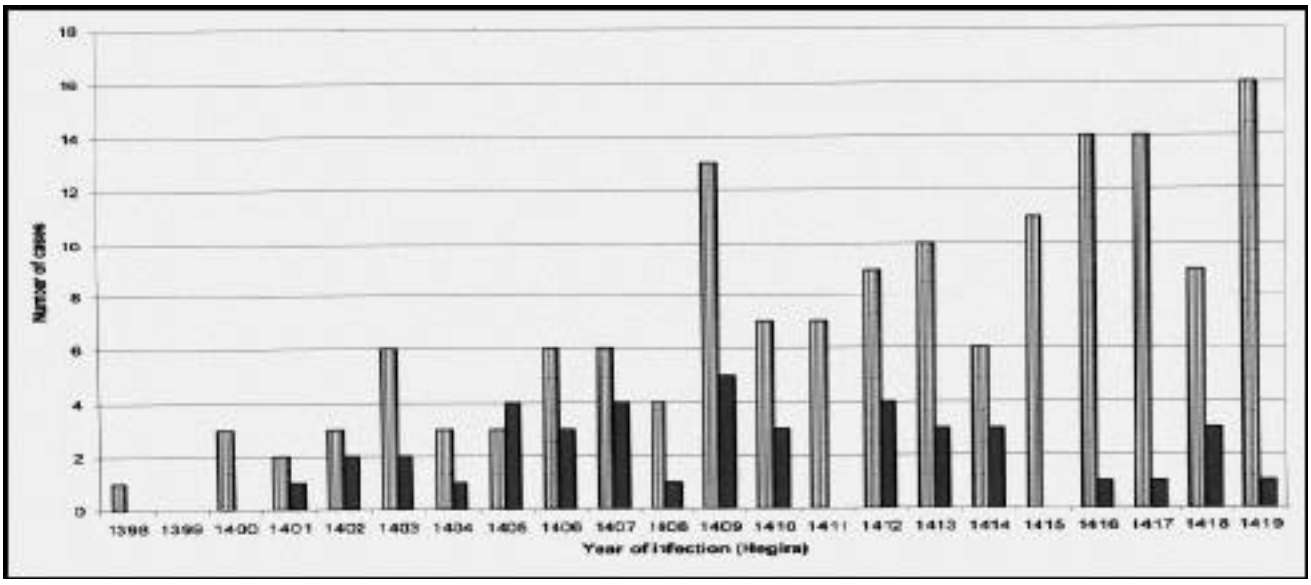

Figure 1 - The distribution of malaria cases in relation to year (Hejira). There is a progressive increase in cases diagnosed, separated into naturally acquired (cross-hatched bars) and blood transfusion induced (solid bars) except in 1409 when a high peak was observed. There is apparently no correlation between naturally acquired infections and blood transfusion induced malaria.

Table 4 - Malaria infections, hospital discharges and red blood cells concentrates transfused, 1410-1419H.

Year of infection (Hejira)	**1410**	**1411**	**1412**	**1413**	**1414**	**1415**	**1416**	**1417**	**1418**	**1419**
All infections	10	7	9	16	9	12	15	15	20	18
Natural infections	7	7	5	9	6	12	14	14	17	17
Transfusion related infections	3	0	4	3	3	0	1	1	3	1
Red blood cell transfused (x 10^3)	11.6	11	15.5	16.9	18.5	19.8	19.4	19.1	20.9	15.6
Hospital discharges (x 10^3)	15.5	12.7	15.2	17.6	18.3	19.5	20.5	21.6	21.9	22.6

Table 5 - Primary diseases complicated by transfusion-associated malaria.

Hematological		**Surgical**	
Acute leukemia	8	Valve replacement	8
Sickle cell anemia	4	Renal transplant	8
Thalassemia major	2	Liver transplant	1
Hemolytic-uremic syndrome	1	Thyroid carcinoma	2
Immune deficiency	3	Ewing's sarcoma	1
Lymphoma	3	Breast carcinoma	1
Bone marrow transplant	2		
Total	**23**		**21**

their infection through this route. It is interesting that clustering of iatrogenically acquired malaria has not been previously reported elsewhere, with the possible exception of the highly unusual report from Riyadh, KSA in which use of contaminated hypodermic injections was the source of several infections in a neonatal unit.[2] *Plasmodium falciparum* was the most frequently identified organism, accounting for 152 (74.2%) of 205 classifiable cases, with *P. vivax* following as a distant second with 52 (25.4%). By comparison, *P. falciparum* accounted for 17,340 cases from a total of 19,623 (88.4%) reported for the whole of KSA in 1992.[14] The annual frequency of malaria in this hospital appears to have increased between 1398 and 1419H. The reason for this increase is not known for certain. Although it could be related to better detection, it seems likely that the increase could merely reflect the increase in the number of all types of patients being admitted to the hospital. The majority of patients acquired their infection in a natural way through mosquito bites, with one subset by virtue of residence in an endemic area and another through travel to one. The majority in this latter group were non-Saudis, consisting mostly of Sudanese. The non-Saudis seen are part of a highly restricted group consisting mostly of KFSHRC employees and their families originating from, or travelling to endemic areas outside KSA. As noted earlier, 33 of the 44 (75%) patients who had transfusion-acquired malaria were Saudis ($x^2 = 11.0$, $p<0.001$). On the other hand, Saudis constituted only 40.1% of all patients with naturally acquired infection. The exact reason for this disproportion is not clear, but could be due to the fact that the base patient population at KFSHRC are Saudis. Another striking observation is that males exceeded females by a factor of nearly 3 ($p<0.001$), for which we have no explanation. The admission pattern of patients to the hospital shows no disproportion in favor of males, compared to females. It is axiomatic that the majority of patients with BT-acquired malaria would have had an intercurrent illness. Although being sick means a higher probability of being transfused, it is worth noting, nevertheless, that the background illnesses in our patients were conditions in which an immune deficit may have been present. Included among these, and as reported elsewhere, were leukemia,[9-11,15] sickle cell disease, thalassemia major,[16,17] post-splenectomy,[16,18] heart disease requiring open-heart surgery,[19-22] other malignancies[23-25] and prematurity.[12,26] The range of underlying conditions is similar to that reported in 12 patients by Mohareb[13] from another institution in Riyadh, KSA. Combining these 2 series, a total of 58 patients with BTIM had reason for immune compromise. Due to the retrospective nature of our analysis, it is not possible to determine the respective roles of immune compromise versus extent of exposure to blood transfusion, although our data shows that for BTIM, there is no relationship between the rate of transfusion and the frequency of transfusion-acquired malaria. Given this, it could be that the immunologically compromised cohort in our series was probably more likely to develop clinical malaria when challenged by infected blood. Although, the immunological interaction between host and malaria parasite is complex, both antibody and cell mediated function are required for protection. This is clear in avian and murine experimental models.[27] Thus, if either arm is impaired as could occur in categories of illness experienced by our patients, clinical infection could more easily manifest. There is currently no universally acceptable in-vitro test for detecting low-level parasitemia in the asymptomatic prospective blood donor. Whilst donors suspected of being a source of BTIM may be serologically investigated, post-facto, for anti-malaria antibodies, either by immunofluorescence assay[28] or by enzyme linked immunoassay,[29-30] this approach may be too non-specific to allow for its use in pre-transfusion screening of donor blood. Evaluation for malaria antigen by immunological methods[31] has not yet received extensive validation. Screening by microscopic examination of blood smears is far too inefficient for widespread application. Instead, uniform standards for exclusion by clinical history, are recommended by some regulatory authorities such as the American Association of Blood Banks.[32] However, the adequacy of a 3 year exclusion period stipulated by these standards, has been called into question by some,[33] although others[34] have advocated a relaxation. The fact that malaria could remain dormant, and presumably asymptomatic for as much as 40 years,[35] provides reason for a more cautious approach. In the United States of America, *P. malaria* has been the most frequently implicated organism in transfusion associated malaria,[34,36,37] presumably due to its ability to remain dormant for extremely long periods.[35] In our study, only one instance of *P. malaria* infection was observed and this was via a natural route. *Plasmodium falciparum*, not subject to hypnozoic hibernation or prolonged dormancy, was the most common in BTIM, which emphasizes that the role of dormancy or the hypnozoic state in donor risk potential may be marginal in our setting. Recently, automated blood cell counters have been shown to be capable of detecting malaria parasite infection by exploiting the ability of malaria pigment to depolarize light,[38-39] and also by their ability to detect cellular deoxyribonucleic acid.[40] If such instruments prove sensitive enough in the setting of donor blood screening, then the risks of malaria transmission by BT may be reduced. For the present, however, the only way of preventing BT transmitted malaria is excluding all donors who have ever lived or travelled to endemic areas. But such a policy could seriously limit the availability of blood in endemic areas, or

those adjacent. In the circumstances, restricting the use of blood transfusion to an absolute minimum would seem the most prudent policy.

Acknowledgment. The authors are grateful to Professor Mustafa A.M. Salih for reviewing the manuscript and for his many helpful suggestions.

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