Clinical and laboratory aspects of malaria among children with fever in a low transmission area of Sudan

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الجوانب السريرية والمختبرية للملاريا بين الأطفال المصابين بالحمى في منطقة يتدنَّى فيها معدل انتقال المرض في السودان

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الخلاصة: تم من خلال دراسة مستعرضة، استكشاف الجوانب السريرية والمختبرية لمرض الملاريا بين الأطفال الذين راجعوا مستشفيَيْن للأطفال في ولاية الخرطوم بسبب إصابتهم بالحمى، وذلك خلال موسم انخفاض معدل انتقال هذا المرض. ومن بين 655 مريضاً كانوا يعانون من الحمى، سُجِّل 35.9٪ منهم على أنهم مصابون بالملاريا وذلك بناءً على نتائج الفحص المختبري الذي أجري لهم في المستشفى. إلا أن إعادة فحص الشرائح المخبرية، في المختبر المرجعي التابع للبرنامج الوطني لمكافحة الملاريا، أكدت وجود المرض في 32.8٪ فقط من بين أولئك الذين شُخصت حالاتهم بأنهم مصابون بها، وذلك على مستوى المستشفى. وقد أوضح تحليل الأعراض والعلامات المرضية وجود تباين كبير في العوارض السريرية (الإكلينيكية) التي قدموا بها إلى المستشفى. وعلى الرغم من أن بعض النتائج جاءت مرتبطة بالملاريا، إلا أن إنشاء خوارزميَّة algorithm سريرية دقيقة كان أمراً صعباً. لذلك، فإن هناك حاجة لتوجيه مزيد من الاستثمارات لتحسين المرافق المجهرية التشخيصية في المستشفيات المحلية للتغلُّب على مشكلة المبالغة في تشخيص الملاريا.

ABSTRACT A cross-sectional study explored the clinical and laboratory aspects of malaria among children presenting with fever to 2 paediatric hospitals in Khartoum state during the low transmission season. Out of 655 febrile patients, 35.9% were recorded as having malaria based on hospital laboratory results. However, re-examination of slides at the National Malaria Control Programme referral laboratory confirmed malaria in only 32.8% of those diagnosed with malaria at hospital level. Analysis of symptoms and signs revealed great variability in clinical presentation. Although some findings were associated with malaria, developing a sensitive clinical algorithm was difficult. Further investment is needed to improve microscopic diagnosis facilities in local hospitals to overcome the problem of over-diagnosis of malaria.

Aspects cliniques et biologiques du paludisme chez les enfants ayant de la fièvre dans une zone de faible transmission au Soudan

RÉSUMÉ Une étude transversale sur les aspects cliniques et biologiques du paludisme chez les enfants ayant de la fièvre a été réalisée dans 2 hôpitaux pédiatriques de l'État de Khartoum pendant la saison de faible transmission. Sur les 655 patients fébriles, 35,9 % ont été recensés comme étant atteints de paludisme en se fondant sur les résultats de laboratoire de l'hôpital. Toutefois, le réexamen des lames au laboratoire de référence du Programme national de lutte antipaludique a confirmé le paludisme chez seulement 32,8 % des enfants diagnostiqués avec le paludisme au niveau hospitalier. L'analyse des symptômes et signes a révélé une grande variabilité dans le tableau clinique. Bien que certains résultats soient associés au paludisme, il a été difficile d'élaborer un algorithme clinique sensible. Un investissement supplémentaire est nécessaire pour améliorer les moyens de diagnostic microscopique dans les hôpitaux locaux afin de surmonter le problème du diagnostic par excès du paludisme.

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Introduction

Malaria remains a public health problem worldwide with the majority of cases and deaths seen in Sub-Saharan Africa [*1,2*]. On average, an African child experiences 6 episodes of malaria a year and almost 1 million deaths occur annually among children [*3,4*].

Malaria in Sudan accounts for 20%–40% of the total attendances at outpatient departments and around 30%–40% of hospital admissions, with an annual reported 4 million cases and 4000 deaths on average. *Plasmodium falciparum* is the predominant species and the dominant malaria vectors include *Anopheles arabiensis, A. gambiae* and *A. funestus* [unpublished report, National Malaria Control Programme, Sudan]. In Khartoum state, malaria is classified as hypoendemic with 2 peaks, 1 in the rainy season and 1 in the winter. Early in the last century (1904), the Khartoum area was declared malaria-free after the use of very simple measures for larval control [*5*]. As a result of internal displacement of the population, massive urbanization with expansion of the city limits, an influx of refugees and deterioration in the malaria control programme, the situation has worsened greatly during the last 20 years. In 2001 and 2002, there were 908 923 and 759 305 cases of malaria respectively recorded in the area [*6*]. The majority were the result of infection with *P. falciparum* (85.6%), with a small proportion due to other species (*P. vivax* 8.2% and *P. ovale* 6.2%) [*7*].

Children with malaria usually present with fever and other symptoms and signs suggestive of uncomplicated or severe complicated malaria [*8*]. Other common infections in children may lead to these clinical findings; the list includes tonsillitis, pneumonia, urinary tract infection, dysentery, septicaemia and meningitis. It is difficult therefore to diagnose malaria with confidence without a high index of suspicion and supportive (reliable) laboratory results. Although laboratory confirmation is essential where facilities are available, better clinical definition has been found to improve the specificity of malaria diagnosis especially in areas of low endemicity [*9*].

In Sudan, the majority of registered malaria cases are clinically diagnosed. In addition to the over-reliance of health workers on clinical judgement, there is the problem of low specificity and sensitivity of microscopic diagnosis of malaria in local hospitals [*6,10*]. Malaria case management in the Khartoum area is delivered by health workers in over 500 public, private and non-governmental organization health facilities. The majority of these lack proper facilities for microscope examination of slides. Due to lack of referral arrangements, these hospitals take a considerable burden of uncomplicated as well as of severe complicated malaria.

This study in Khartoum was conducted to assess the association between certain clinical/laboratory findings and malaria among children in an urban area with low malaria transmission. This may help in developing a sensitive clinical algorithm for the diagnosis of malaria.

Methods

Study setting

Khartoum, the capital of Sudan, has a population of around 5 million, distributed over 28 000 km^2. This cross-sectional facility-based study was conducted in 2 teaching paediatric hospitals, chosen intentionally out of 6 paediatric hospitals in the area, during the period 7 January to 31 March 2002.

Sample

The sample was drawn from children aged from 2 months to 16 years who presented to the outpatient department of the 2 participating hospitals with fever or a history of fever within the past 72 hours. Patients with a problem obviously not suggestive of malaria and patients with criteria suggestive of severe malaria were excluded. The minimum sample size was estimated to be 400 children divided over the 2 hospitals [*11*]. The calculation was based on an estimation that 50% of hospital attendances were suspected malaria, targeting 95% confidence interval (CI). In each hospital, 2 full working days per week were assigned for the study during the study period.

Clinical data

A pre-tested pre-coded questionnaire was used to record personal data about patients, signs and symptoms and the results of laboratory examinations. In each hospital, a trained paediatric registrar, assisted by a house officer, collected the data. Verbal consent for participation was obtained from the patient or caretaker, before taking a history and making a clinical examination. The selected child was seen first by the house-officer and then by the registrar. For children who could not respond properly, data were collected from their mothers or any other caretakers with them. Each patient was then sent to the hospital laboratory for investigation of peripheral blood films for malaria and measurement of haemoglobin level. The results of the laboratory investigations were recorded on a special form and then incorporated into the patient questionnaire.

Laboratory tests

Blood samples were obtained from all children for examination for malaria parasites. For microscopic diagnosis of malaria, thin and thick blood films were stained using 10% Giemsa stain. Hundreds of fields were examined at 10×100 magnification under oil immersion by trained malaria microscopists for the presence of trophozoite and gametocyte stages, and for identification of parasite species. The density was estimated by counting the number of asexual parasites per 200 white blood cells and then multiplied by 40 to get the parasite number per 8000 white blood cells.

As the "gold standard" for malaria diagnosis, all blood films were re-examined under the supervision of a senior parasitologist at the National Malaria Control Programme referral laboratory. Haemoglobin level was estimated colorimeterically using Drabkin's solution.

Malaria cases were defined as patients with any degree of parasitaemia as confirmed by the referral laboratory. The rest of the cases were considered as fever due to other diseases and used as controls in the odds ratio (OR) analysis of symptoms and signs.

Data analysis

The questionnaires were collected on a weekly basis and entered into a computer and analysed using *SPSS*, version 10.0, and *Epi-Info*, version 6.04b software. Tables or figures were generated as appropriate. Frequencies were compared using the chi-squared test. OR with 95% CI were used to assess the association between various clinical laboratory findings and malaria. The OR for clinical and laboratory findings were calculated for all children and for children under 5 years old.

Results

During the study period 655 febrile patients were enrolled in the study. Their ages varied between 2 months and 16 years, with a

mean (standard deviation) age of 49.7 (45.2) months. Children under 5 years were 65.8%. The male to female ratio was almost 1:1. All were resident in Khartoum state, distributed over 5 provinces.

Laboratory results

Of the patients 35.9% (235/655) were identified as having malaria based on hospital laboratory results. Re-examination of the slides at the National Malaria Control Programme referral laboratory revealed a slide positive rate of only 11.7%, i.e. only 32.8% (77/235) of slides assigned as positive at hospital level (Table 1). Nevertheless, 6 cases of malaria were missed (assigned as negative for malaria by the hospital laboratories). The overall specificity for the hospital laboratory testing was 73% and the sensitivity was 90%.

Almost 50% of slides examined in 1 hospital were judged positive compared with 12.4% at the referral laboratory, whereas at the other hospital only 17.8% of slide were positive versus 10.9% at the referral laboratory. Therefore the false-positive rate was very different at the 2 hospitals (61.2% versus 25.2%) (Table 1).

All the parasites identified were *P. falciparum*. Parasite counts was made at the referral laboratory only; no patient had a parasite count above 100 000 parasites/µL and only 12.9% had less than 1000 parasites/µL. The majority (87.1%) had between 1000 to 100 000 parasites/µL.

Signs and symptoms

Fever, as perceived by the patient or caretaker, was the admission criterion. An axillary temperature of ≥ 37.5 °C was found in 254 (38.8%) of all patients. For cases with true-positive slides, an axillary temperature of ≥ 37.5 °C was found in 23 patients (29.9%), reflecting the intermittent nature of fever in malaria. The other symptoms, signs and laboratory results were seen with different frequencies (Table 2). Intermittent fever, headache, irritability, cough, ill appearance and axillary temperature ≥ 37.5 ºC were the criteria seen in more than 60% of patients, followed by rigours, vomiting and runny nose which were seen in more than 50% of patients; other criteria were seen in less than 30% of patients.

Odds ratio analysis

According to the results of the referral laboratory, patients were classified into those with blood films positive for *P. falciparum* (malaria patients) and no positive films

Table 1 **Malaria slide positive rates and the specificity and sensitivity of local hospital test results for children presenting with fever to paediatric hospitals in Khartoum state**

Hospital	Total slides tested No.	Referral laboratory[a] Slides positive No.	Hospital laboratory Slides positive No.	Missed cases No.	Specificity %	Sensitivity %
Hospital A	380	47	186	1	58	98
Hospital B	275	30	49	5	90	83
Total	655	77	235	6	72	92

[a]*Gold standard.*

Table 2 **Frequency of various signs and symptoms among children presenting with fever to paediatric hospitals in Khartoum state**

Variable	No. (*n* = 655)	%
Ill appearance	535	81.7
Irritability	464	70.8
Intermittent fever	516	78.8
Headache	223[b]	69.7
Cough	429	65.5
Axillary temp. ≥ 37.5 °C	401	61.2
Nausea or vomiting	385	58.8
Generalized aches	160[a]	54.2
Runny nose	345	52.7
Fever with rigors	340	51.9
Poor feeding/failure to suck	139	21.2
Urinary complaints	128	19.5
Crepitations	116	17.7
Pale appearance	115	17.6
Blood film +ve for ***P. falciparum***	77[c]	11.8
Convulsions present/ recent history	64	9.8
Earache	49	7.5
Dehydration	46	7.0
Splenomegaly	45	6.9
Bloody diarrhoea	44	6.7
Fast breathing	41	6.3
Haemoglobin ≤ 6 g/dL	37	5.6
Difficulty in breathing	35	5.3
Hepatomegaly	28	4.3
Nasal flaring	15	2.3
Wheeze	24	3.7
Rash	15	2.3
Grunting	8	1.2

n ***= total number of patients examined.***
[a]***Applicable for 295 patients.***
[b]***Applicable for 320 patients.***
[c]***Based on referral laboratory re-examination.***

(control patients) and the odds ratio analysis was made on this basis. Each case had 8 controls, matched with respect to mean age ($P = 0.84$), mean weight ($P = 0.32$) and sex ($P = 0.067$).

For malaria among all ages, out of the long list of symptoms and signs, no clinical or laboratory feature was found to be positively associated with slide-positive malaria, with the exception of inability to feed (OR 1.92).

The following signs were found to be significantly negatively associated with slide-positive malaria: having fever with rigours (OR 0.71), irritability (OR 0.86), running nose (OR 0.82), ill appearance (OR 0.88), axillary temperature ≥ 37.5 °C (OR 0.82), no grunting (OR 0.98), no rash (OR 0.97) and haemoglobin ≤ 6 g/dL (OR 0.36). Analysis of the data related to children less than 5 years showed a significant negative association between malaria and having fever with fast breathing, running nose, no grunting, no rash, haemoglobin ≤ 6 g/dL and being a female (Table 3).

None of the cases with grunting or rash had malaria and a minority of those with earache (10.2%), flaring nose (13.3%) or wheezes (4.2%) had positive blood films for *P. falciparum* (Table 3). As regards the high false-positive rates at of both hospital laboratories, it was found that 31 patients with the above symptoms/signs were treated as malaria although they had a clear cause for the fever.

Discussion

Early diagnosis and appropriate treatment of malaria cases is recognized by the World Health Organization (WHO) as an important strategy to reduce suffering and death from malaria [*1*]. This implies that mothers and patients are able to recognize the clini-

Table 3 **Odds ratios for various signs, symptoms and laboratory findings among children diagnosed with malaria at paediatric hospitals in Khartoum state**

Clinical/laboratory finding	Malaria among all children		Malaria among < 5-year-old children	
	No.	OR (95% CI)	No.	OR (95% CI)
Inability to feed/poor feeding	9	1.92 (1.02–3.62)*	6	1.96 (0.91 - 4.25)
Splenomegaly	4	1.36 (0.50–3.70)	2	1.28 (0.30–5.32)
Urinary complaints	12	1.28 (0.74–2.22)	9	1.09 (0.58–2.04)
Bloody diarrhoea	24	1.18 (0.51–2.41)	5	0.70 (0.29–1.69)
Earache	5	1.17 (0.48–2.86)	3	1.45 (0.60–4.55)
Hepatomegaly	3	1.11 (0.34–3.59)	2	1.02 (0.24–4.32)
Dehydration	5	1.09 (0.44–2.68)	5	1.05 (0.43–2.53)
Convulsions	7	1.08 (0.51–2.29)	6	0.77 (0.34–1.73)
Not cyanosed	74	1.00 (0.96–1.05)	47	0.99 (0.93–1.06)
No grunting	77	0.98 (0.97–0.99)*	49	0.98 (0.97–0.99)*
No wheezes	76	0.97 (0.94–1.00)	48	0.97 (0.92–1.01)
No crepitations	65	0.97 (0.87–1.07)	43	0.91 (0.81–1.02)
No rash	77	0.97 (0.96 -0.98)*	49	0.96 (0.95–0.98)*
Intermittent fever	64	0.94 (0.84–1.05)	40	0.91 (0.79–1.06)
No cough	28	0.94 (0.68–1.29)	17	0.85 (0.56–1.29)
Nausea or vomiting	48	0.94 (0.78–1.13)	30	0.95 (0.75–1.21)
Ill appearance	70	0.88 (0.82–0.96)*	43	0.96 (0.86–1.08)
Nasal flaring	2	0.86 (0.19–3.76)	2	0.64 (0.14–2.84)
Irritability	62	0.86 (0.76–0.98)*	41	0.91 (0.79–1.04)
Sex (female)	43	0.82 (0.66–1.02)	29	0.75 (0.57–0.96)*
Running nose	48	0.82 (0.68–0.99)*	36	0.80 (0.66–0.96)*
Axillary temp ≥ 37.5 °C	50	0.82 (0.68–0.98)*	30	0.87 (0.68–1.11)
Difficulty in breathing	5	0.79 (0.32–1.99)	3	1.02 (0.32–3.28)
Pale	17	0.76 (0.48–1.71)	12	0.81 (0.47–1.38)
Rigors	54	0.71 (0.59–0.83)*	29	0.77 (0.60–1.00)
Fast breathing	8	0.55 (0.26–1.14)	8	0.46 (0.22–0.96)*
Haemoglobin ≤ 6 g/dL	10	0.36 (0.18–0.71)*	8	0.35 (0.16–0.74)*

P < 0.05.
OR = odds ratio. CI = confidence interval.

cal presentation of malaria and are able either to treat it themselves or to consult a nearby health facility or health personnel. This approach (home-based malaria management) has proved feasible and cost-effective in many parts of the world [*12*]. On the other hand, health personnel should be able to differentiate between malaria and other causes of fever in areas where there are no facilities for microscopic diagnosis.

At present in Sudan, according to the National Malaria Control Programme, all fevers are presumed to be due to malaria, unless proven otherwise [unpublished report, National Malaria Control Programme, Sudan]. The guidelines recommend blood films to confirm the presence of malaria parasites, especially in areas of low malaria transmission.

It is clear from the results of this study that the diagnosis of malaria in children in the study area is difficult without good laboratory support. Over-diagnosis and hence over-treatment was a feature of this study, with a risk of missing other fatal diseases in children, such as pneumonia. Only 32.8% of those diagnosed as having malaria at the hospital laboratory were confirmed positive from blood films at the referral hospitals, reflecting a very low specificity of diagnosis based on clinical signs. Studies carried out in Sudan and other developing countries have revealed the same pattern [*10,13,14*]. The monitoring data for 2003 provided by the Sudan state malaria control programme confirmed this and showed a poor level of specificity at the hospital laboratories. A total of 14 878 positive and negative slides were cross-examined; out of 4106 slides assigned as positive by the laboratory technicians at health facilities level, 55.5% were false-positives [personal communication, Ministry of Health, Khartoum]. The control programme in the state carried out a series of training and supervision activities, but the situation is still far from satisfactory and is further jeopardized by poor control over the growing private sector. It is worth investing more in improved diagnosis, as this has been shown to save considerable amounts of patient time and money [*15*].

Clinical observations collected from patients admitted into this study complicated the situation of poor laboratory diagnosis. With the exception of grunting and rash, all clinical presentations were seen in malaria patients but only a few criteria out of 26 clinical criteria showed a significant association with malaria. Even so, these are symptoms which are difficult to obtain from the patient or to assess by the caregivers. The only reliable criterion that can be used to support the diagnosis of malaria is a haemoglobin level ≤ 6 g/dL.

It seems that the differentiation of malaria from other causes of fever depending on clinical observation in the absence of microscopy is difficult in low transmission areas such as Khartoum. Some studies carried out in this field agree with the above conclusion [*15,16*] but others suggest that diagnosis of malaria can be predicted by better clinical definition and identification of a mixture of symptoms, signs and laboratory tests [*17–20*], and unpublished report, National Malaria Control Programme, Sudan]. The commonest findings identified by the latter studies include: confirmed fever, headache, generalized aches, splenomegaly, pallor and low haemoglobin level.

In summary, the identification of children who need anti-malarial drugs is difficult based on clinical findings alone in settings with low malaria transmission such as Khartoum. The efforts of the Khartoum Malaria Free Project (a partnership between Khartoum state Ministry of Health, the National Malaria Control Programme and WHO) should be directed towards improvement of microscopic diagnosis of malaria in local hospitals and to address the possibility of using rapid diagnostic tests to avoid malaria over-diagnosis.

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Second Workshop on the Child Health Policy Initiative to be held in Cairo, Egypt, 13–16 November 2005

The Child Health Policy Initiative (CHPI) was launched by the World Health Organization's Regional Office for the Eastern Mediterranean in October 2003. Five countries, Egypt, Morocco, Sudan, Syrian Arab Republic and Tunisia, joined the first phase, during which a thorough situation analysis was carried out to identify key policy issues to be addressed in the national child health policy document. A first workshop on CHPI was held in Damascus in July 2004 to review progress of work in those 5 countries. As part of the initiative, the Regional Office developed the document *Development of National Child Health Policy - Phase 1: the Situation Analysis*. This second workshop aims to review the child health situation analysis reports developed by the 5 countries and plan for the next steps leading to the development of the national child health policy documents. The experience will be shared with other countries in the Region which have expressed interest in joining the initiative, namely Iraq, Jordan, Oman and Pakistan.