Published in final edited form as:
J Travel Med. 2010 September ; 17(5): 334–338. doi:10.1111/j.1708-8305.2010.00434.x.

Pediatric malaria: 8 year case series in Atlanta, Georgia, and Review of the Literature

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Abstract

Background—Although malaria is frequent in travelers, it is often misdiagnosed on initial presentation, especially in children. The objective of this study is to describe epidemiology, clinical and laboratory presentation, and treatment of children with malaria in the United States.

Methods—We performed a retrospective review of 50 confirmed cases of malaria from 2 pediatric metropolitan hospitals in Atlanta, GA from 2000 – 2008.

Results—Malaria smears were performed in 385 unique patients; 50 (12.6%) were positive. American children who had visited family and friends in malaria endemic countries comprised 62% of our cases. Most cases visited Nigeria or Cameroon; all but 3 travelled to Africa. Three patients presented 8 – 12 months following travel. *Plasmodium falciparum* was diagnosed most frequently (72%). Most patients had low level parasitemia (<1%). Gametocytes were rarely identified. Treatment was primarily with quinine and either doxycycline or clindamycin, transfusion was rare. All patients responded rapidly to treatment. Although 7 (14%) had hyperparasitemia (>5%), no fatalities or long-term sequelae were seen.

Conclusions—Malaria diagnosis can be difficult in children because parasitemia is usually below 1%. A high index of suspicion is required in patients who have travelled to Africa.

Keywords

Malaria; Pediatric; Imported; United State

About 1500 cases of imported malaria are reported annually in the United States,1 and the true number of cases is likely higher.2 Although malaria is one of the most common causes of fever in returned travelers,3›4 it is misdiagnosed as often as 90% of the time on initial presentation in children since parents of these young travelers do not perceive malaria as a true threat and frequently fail to provide adequate travel history to the health care provider.5 This lack of perception of threat also increases the risk of acquiring malaria since these children are rarely given adequate prophylaxis.6–11

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Declaration of Interests
The authors state that they have no conflicts of interest.

Mortality due to malaria in the US (among all ages) is generally low (~1%), but delays in diagnosis and treatment may lead to fatalities.12 Of 123 fatal cases seen in the US from 1963–2001, 109 had seen a doctor prior to death but 33 received no or inadequate treatment, either because the diagnosis was not made, there was a delay in initiating treatment, or the treatment was inadequate for the species or region where the traveler had been.12

US clinicians and laboratories need to be familiar with the epidemiology, signs and symptoms, laboratory diagnosis, and treatment of malaria in young travelers to adequately diagnose and institute chemoprophylaxis. Here we present our experience with 50 children seen at one institution (comprised of 2 pediatric hospitals) and compare our results to what has been published in the literature. We also review the treatment that children should be receiving once the diagnosis of malaria has been made.

Methods

We conducted a retrospective review of all cases of microscopically confirmed malaria diagnosed by the Children's Healthcare of Atlanta (CHOA) laboratory from 1/1/2000 until 12/31/2008. CHOA consists of two children's hospitals with a total of 474 beds serving the greater metropolitan Atlanta area, which has a population of 5.1 million people.13 Each hospital has a core laboratory with microscopy for manual differential blood cell counts and malaria thick and thin smears.

Using the laboratory information system, we searched for all patients less than 18 years old for which malaria testing had been ordered. Laboratory confirmation required identification of malarial forms on Giemsa stained thick or thin smear; all slides were reviewed by 2 technologists and a microbiology PhD proficient in identifying malaria parasites. Parasitemia was reported as a percent of parasitized red blood cells (one erythrocyte parasitized with more than 2 parasites is counted as one) after counting 4000 cells.

All charts were abstracted by both reviewers to a standardized data abstraction form and discrepancies in interpretation were resolved by review and discussion of the information in question. Data were analyzed using Microsoft Excel (Seattle, WA) and SAS version 9.1.3 (Cary, NC). Descriptive statistics were calculated on all patients for whom data were available. The CHOA Institutional Review Board approved this study.

Results

Study Population

We identified a total of 50 children with blood smear confirmed malaria out of a total of 385 children who had malaria smears performed during the study period. Three children had smears sent twice, several years apart. Only 3% (10 children) without malaria had more than one slide sent. The mean age of infected children was 8.1 years (1.1–16.8 years, interquartile range 6–10 years), 60% were boys.

In 42 patients a travel reason was recorded, 15 patients (37%) had been living abroad (8 immigrants, 5 refugees, 2 visitors from abroad to the US) while 26 (62%) were US citizens visiting friends and relatives in the country of the parents' origin. One patient was travelling for other reasons. The median duration of travel was 30 days (14 – 75 days). The median time from arrival in the US until presentation was 10 days, with 25% of children presenting within 7 days (1–365 days, N=37). Most cases presented in the summer (May to August). None of the cases presenting after 28 days had *P. falciparum* malaria. Two cases presented a year after travel; one with *P. vivax* and the other with *P. ovale*. A previous history of malaria

was reported in 73% of patients (22/30 patients); however, it is unclear whether these represent presumptive or microscopic diagnoses.

Countries Visited

In Table 1 we show the countries visited by the 43 children for whom we have travel data. Of note, 93% reported travel to Africa, Nigeria was being the most commonly visited country (51%), followed by Cameroon (14%); all other countries accounted for only 1–2 cases. Only 2 cases presented from the Americas: one from Haiti presented with *P. falciparum*, while the other, from Guatemala, presented with *P. vivax*.

Presenting Symptoms

Fever was the most common symptom, present in 97.6%, followed by vomiting (34%). Fever was present for a mean of 4 days (1–11 days) prior to presentation. Hepatomegaly was present in 28%, splenomegaly in 20%. Headache was reported in 20% of patients, all of the patients with headache also reported fever. Abdominal pain was reported in 20%; one patient reported abdominal pain without fever. Diarrhea was present in 3 cases, all had fever but only one reported vomiting, none reported abdominal pain. Myalgias were reported in 10% and malaise or fatigue in 6%. Three patients presented with sore throat and fever, one of whom also had vomiting. Three patients had jaundice. One patient had altered mental status on presentation.

Prophylaxis

Only 10 patients (20%) had taken any prophylaxis to prevent malaria. Five of these took a drug that was inappropriate for the country to which they traveled.

Laboratory findings

Plasmodium falciparum was most common (74%). *P. vivax*, *P. ovale*, and *P. malariae* were present in 5, 3, and 1 case, respectively. In 4 cases, definitive species identification was not possible due to the low percent parasitemia, with just a few ring forms present. No co-infections were seen. The majority of patients (52%) had parasitemia <1%; only 7 patients had hyperparasitemia (>5%). The maximum parasitemia was 28.6%. All cases with >5% parasitemia were *P. falciparum*. Non-falciparum forms made up 42% of patients with ≤1% parasitemia and 12% of those with 1–5% parasitemia. Gametocytes were rarely identified.

Laboratory results are presented in Table 2. Thrombocytopenia and anemia were the most commonly observed laboratory abnormalities. Mild hyponatremia was also relatively common (36% had sodium ≤135 mEq/L and 12% had sodium ≤130 mEq/L). G6PD levels were measured in 10 children; only one was G6PD deficient. Six patients were tested for sickle cell disease, all were negative. Two patients had known sickle trait.

Treatment

Thirty-four children (68%) were hospitalized for treatment of malaria, with a maximum stay of 9 days. Among those with *P. falciparum* malaria, 75% were hospitalized; 17% stayed for only one day. Documentation of treatment available in 41 children: 18 patients (44%) received quinine and doxycycline, 8 (19%) quinine/quinidine and clindamycin, 4 (9.7%) received atovaquone-proguanil, 6 (15%) received only one drug (quinine, choloroquine or primaquine), the rest received other combinations. Several children received antibiotic therapy due to concern for additional diagnoses. Sixteen patients had received antimalarial therapy previously, although in some cases this was several months prior.

One patient received a blood transfusion for anemia (hemoglobin 5.4 mg/dl). No exchange transfusions were performed. One patient received platelet transfusion for a platelet count of 32,000. All of the patients recovered without serious complications.

Conclusions

This case series demonstrates the wide spectrum of possible clinical presentations which may be seen with malaria- including vomiting, diarrhea, headache, abdominal pain, etc. Gastrointestinal symptoms can be so severe that an intestinal infection may be suspected. Hepatosplenomegaly may be seen; this was less common in our series than in other reports.[14, 15] In contrast to the report by Viani et al, hyponatremia was not a common finding.[14] One almost universal symptom is fever, either by history or at presentation. Because malaria may present with a wide variety of clinical symptoms, a high index of suspicion is required to ensure prompt diagnosis. Primary care providers seeing patients with a history of fever should always ask about a history of travel and request the appropriate diagnostic tests. Physicians must be aware that late presentations of malaria can occur, and can result in serious disease. In our series we had 2 cases which presented a year after travel, highlighting the need to obtain a travel history including at least the preceding two years. Late presentations of malaria are unlikely to be due to *P. falciparum*, since *P. falciparum* generally presents within 1–2 months of exposure;[16] however, *P. falciparum* has been reported with a remote travel history.[17]

The gold standard for diagnosis of malaria relies on trained microscopists finding parasites in Giemsa stained blood smears. Thin smears are used for speciation and quantification of parasitemia while thick smears concentrate the parasites and may be helpful in detecting low level parasitemias. Three smears are recommended to confirm that the patient does not have malaria; it is interesting to note that in our case series, repeated testing was obtained on only 3% of children. The core laboratory at CHOA uses thick smears for diagnosis and thin smears to determine the parasitemia level. Our laboratory does not use rapid diagnostic tests (RDTs) that enzymatically detect malaria proteins (for example, Binax NOW Malaria Test) or polymerase chain reactions. RDTs, which rely on the detection of either *P. falciparum* specific histidine-rich protein 2 (HRP-2), or the pan-plasmodial parasite lactate dehydrogenase (pLDH) enzyme, provide rapid results, and may be of use in initial diagnosis at centers where malaria microscopy is not available. However, these tests are insensitive at low parasite densities, and a blood smear is still needed for determination of the parasitemia.

In our series, more than half of the children had parasitemia below 1%, and 87% had parasitemia of 5% or less. The very low level parasitemia (<1%) makes the diagnosis of malaria more challenging, because not only does one need to consider the diagnosis, but the laboratory must examine the slides very carefully for the presence of ring forms. Gametocytes were rarely observed; speciation was usually based on other morphological aspects.

All of the patients in our series recovered with no long term sequelae. This is most likely related to the primarily low density parasitemias observed in our study. Possible explanations for this include some degree of immunity as approximately half of all patients gave a history of previous malaria or the fact that some of the children had been partially treated prior to presentation.

In Atlanta, there is a large community of people from Nigeria and families visit friends and relatives as well as having relatives visit their families in the US (2 cases in our series), thus it was not surprising that most of our patient had acquired malaria in Nigeria. It is important for health care providers to know the immigrant composition in the community they serve.

The frequency of the different plasmodia changes depending on the city where the study took place and the population studied, for example, studies from the east cost of the United States, Spain and United Kingdom have found *P. falciparum* in over 70% of their cases while a study from the west cost of Canada found *P. vivax* in 88%.14,15,18,19 To our surprise, we had very few patients from Latin America, even though emigration from Latin America is higher than that from Africa. Another consideration is that travelers that visited friends and relatives are more likely to visit high risk areas and stay longer.

Very little information was available about prophylaxis in our cases; prophylaxis was reported in less than 20% of our cases, similar to findings of other studies.15, 18–21 Furthermore, no one took the prophylaxis in the manner in which it supposed to be taken: 50% took a medication that was ineffective for the area of travel (chloroquine in areas with chloroquine resistant *P. falciparum*), and many families stopped prophylaxis halfway through their stay- rather than completing prophylaxis one week (atovaquone-proguanil) to one month (mefloquine and doxycycline) after having completed their travel. This may be because parents returning to their country of origin are less likely to seek pre-travel health consultation and give their children prophylactic medicines.6–10

All travelers to endemic areas should be counseled about malaria prevention, including using insect repellant containing DEET, insecticide treated bednets, keeping arms and legs covered, sleeping in an air-conditioned room,22 and appropriately using a prophylactic anti-malarial drug. Up to date information on areas where malaria transmission occurs and CDC recommended prophylaxis may be found at: http://www.cdc.gov/malaria/risk_map/ or http://wwwn.cdc.gov/travel/yellowBookCh4-Malaria.aspx. The lack of use of chemoprophylaxis in children may be compounded by drug cost and the perception of low risk by parents and the family members they are visiting.

Chloroquine plus primaquine remains the appropriate choice for *P. vivax* acquired everywhere except Papua New Guinea or Indonesia, where chloroquine resistant *P. vivax* is common. For any malaria acquired in these areas, or for *P. falciparum* acquired in an area where chloroquine resistance is found, there are 4 options for treating non-severe malaria: (1) atovaquone-proguanil (Malarone™, GlaxoSmithKline, Middlesex, United Kingdom), (2) Artemether-Lumefantrine (Coartem™, Novartis Pharmaceuticals Corporation, Basel, Switzerland), (3) quinine plus doxycycline or tetracycline (for children over 8 years old) or clindamycin, or (4) mefloquine (Lariam™, Hoffmann-La Roche Inc. Nutley, NJ). Atovaquone- proguanil is very well tolerated, with a short treatment course of only 3 days; however, it was not available as a formulary medication until very recently which likely explains the infrequent use of this drug in our series. For malaria acquired in an area where chloroquine resistance is found, presumptive treatment for *P. falciparum* should be given until a species identification is made. Speciation is necessary to determine whether infection was due to *P. vivax* or *P. ovale* which have latent liver forms (hypnozoites) requiring treatment with primaquine to prevent relapse. As primaquine can cause hemolytic anemia in patients with G6PD deficiency, it is important to rule this out prior to starting treatment with primaquine. In our series, one patient was apparently successfully treated for *P. falciparum* with primaquine alone, but primaquine is never recommended as single treatment for *P. falciparum* malaria, although it may be used for prophylaxis in selected patients. Although several patients in our series were treated as outpatients, this can not be routinely recommended, as serious complications can arise.

Severe malaria in children occurs in less than 20% of cases.14, 15, 18, 21, 23, 24 Severe malaria is most commonly caused by *P. falciparum* and is characterized by neurological involvement (impaired consciousness, seizures, coma), severe anemia, pulmonary edema or acute respiratory distress syndrome (ARDS), thrombocytopenia, shock, acute renal failure,

metabolic acidosis, or hyperparasitemia (>5% parasitized red blood cells). Patients with severe malaria should always be treated with intravenous therapy, either quinidine or artesunate (intravenous artesunate can be obtained for the treatment of severe malaria through an investigational new drug protocol by calling the CDC malaria hotline at 770-488-7788). In endemic countries, artemisinin combination therapies (artesunate or artemether combined with another anti-malarial) are widely used for severe malaria. Artemisinins were discovered in China in 1972 and are the most effective antimalarial compounds available today. In April 2009, Coartem® (artemether-lumefantrinebecame the first artemisinin combination therapy to be licensed in the US. Coartem® is administered orally as 6 doses over 3 days at 0, 6, 24, 36, 48, and 60 hours; dosing is weight based. Current CDC recommendations for treatment of malaria may be found at http://www.cdc.gov/malaria/pdf/treatmenttable.pdf.

In summary, this series of cases shows that children with malaria present with a variety of signs and symptoms, have usually received incomplete prophylaxis if any at all, and have been diagnosed up to one year after travel. In addition, we compared our data to that published by others and have provided information about treatment and prophylaxis of malaria in the pediatric population.

Acknowledgments

Julie Gutman was supported in part by PHS Grant UL1 RR025008 and KL2 RR025009 from the Clinical and Translational Science Award program, National Institutes of Health, National Center for Research Resources.

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Table 1

Countries visited by 43 children with malaria

	n	%
Africa	**40**	**93**
Africa	1	2
Central Africa	**6**	**14**
Cameroon	6	14
West Africa	**30**	**60**
Senegal	1	2
Guinea	1	2
Sierra Leone	1	2
Liberia	2	5
Ivory Coast	2	5
Nigeria	22	51
Togo	1	2
East Africa	**3**	**6**
Uganda	1	2
Kenya	1	2
Tanzania	1	2
Central America/ Caribbean	**2**	**4**
Haiti	1	2
Guatemala	1	2
Asia	**1**	**2**
Thai/ Burmese border	1	2

Data only available for 43 patients.

Table 2

Clinical and Laboratory Characteristics of patients with Malaria

Variable	N tested	Mean	Standard Deviation	Minimum	Maximum	Normal Range
Age (years)	50	8.1	4.1	1	16	
Fever Duration (days)	31	4.0	2.5	1	11	
Time to presentation (days post travel)	37	37.1	88.4	1	365	
Days Hospitalized	50	0.4	0.5	0	1	
Parasitemia (%)	46	2.8	5.2	0.03	28.6	0
White blood cells on admission (thousand/ul)	40	6.8	3.0	2.6	13.84	4.5–13.5
Absolute neutrophil count on admission (thousand/ul)	37	4.0	2.4	0.99	9.78	1.8–8.0
Platelets on Admission (thousand/ul)	40	151	123	24	611	150–450
Admission Hemoglobin (mg/dl)	49	10.4	1.8	5.4	13.8	13–16
Mean corpuscular volume	47	76.6	7.3	46.1	90.6	78–98
Reticulocyte count (%)	11	2.6	2.1	0.6	8.4	0.5–3
Reticulocyte production index (%)	11	0.7	0.5	0.2	2	0.5–1.5
C-reactive protein (mg/dl)	31	8.0	6.3	1.2	25.4	<1.0
Erythrocyte sedimentation rate (mm/hr)	9	41.3	24.2	10	97	0–20
Creatinine (mg/dl)	36	0.6	0.2	0.3	1.4	0.3–1.0
Albumin (gm/dl)	33	3.2	0.6	2.3	4.6	3.1–4.8
Aspartate amino transferase (U/lt)	35	98.5	229.1	17	1311	13–38
Alanine amino transferase (U/lt)	35	53.5	96.5	7	547	8–36
Bilirubin (total, mg/dl)	34	1.9	2.9	0.2	16.5	0–2
Sodium (mmol/lt)	41	135.3	3.7	122	143	133–143