Rickettsia felis Infection in Febrile Children, Ghana

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Abstract. Rickettsial infections are an underrecognized cause of febrile illness in sub-Saharan Africa. To evaluate the epidemiology and clinical features of rickettsial disease in pediatric patients in Ghana, we screened blood samples from febrile children aged less than 15 years presenting to an outpatient department in Ghana’s Ashanti Region for the presence of rickettsial DNA. We detected Rickettsia felis in 7/470 (1.5%) blood samples, using two independent real-time polymerase chain reactions. No other Rickettsia species were found. R. felis was detected repeatedly in one patient, and coinfection with Plasmodium falciparum was found in 3/7 samples. Symptoms apart from fever included cough (6/7) and vomiting (4/7). None of the R. felis-positive patients reported a rash. This study is the first report on R. felis in Ghana and adds to the growing evidence for its widespread occurrence with and without malaria coinfection in sub-Saharan Africa.

Systemic bacterial infections have been found to contribute substantially to the causes of febrile illnesses in sub-Saharan Africa (SSA). In blood cultures, Salmonella enterica, Streptococcus pneumoniae, Staphylococcus aureus, and Escherichia coli are the most common pathogens.1 Bacteria requiring more elaborate diagnostic techniques such as Rickettsia, are still underdiagnosed despite their public health importance.2 Besides typhus group and spotted fever group rickettsiae, Rickettsia felis has recently been found to be potentially widespread in SSA, where R. felis-specific circulating DNA has been detected in the blood of up to 15% of febrile patients from Mali, Senegal, Gabon, and Kenya.3–5 However, its role as a pathogen is still unclear and data on the geographical distribution, epidemiology, and clinical features of R. felis are limited. In West Africa, R. felis has only been reported in patients from the Sahel-zone countries of Mali and Senegal.4,6 Since appropriate diagnostic methods are largely unavailable and standard antibiotic regimens usually do not cover Rickettsia spp.,7 further data are critical to aid physicians in the empirical management of febrile illness.

We screened blood samples from febrile children to evaluate the epidemiology and clinical features of rickettsial disease in Ghana.

Recruitment took place at St. Michael’s Hospital, Pramso, located in the suburban belt of Kumasi, the capital of Ghana’s Ashanti Region, where malaria is endemic with high transmission intensity throughout the year.8 Venous blood was taken from all children below 15 years of age visiting the outpatient department with fever ≥ 38°C (tympanic) between January and December 2012. Blood cultures and malaria microscopy (thick and thin films) were done at each presentation and a blood sample (ethylene-diaminetetraacetic acid [EDTA]) was stored for further diagnostics. Rickettsia polymerase chain reaction (PCR) was performed on 470 randomly selected blood samples, from patients with negative blood cultures and reporting regular contact with domestic animals.

For molecular diagnosis of Rickettsia spp., total DNA was extracted from EDTA-blood and tested by real-time PCR targeting the rickettsial gltA gene, using previously reported oligonucleotides.8 The amplicons were bidirectionally sequenced (SeqLab, Göttingen, Germany) and were 100% identical with R. felis upon BLAST analysis (https://blast.ncbi.nlm.nih.gov/Blast.cgi). Species identification was confirmed using a second real-time PCR specific for the ompB sequence of R. felis (see Supplemental Material for details on molecular methods).10 No other Rickettsia species were found.

In total, 470 blood samples from 431 individuals were tested. Of the 431 individuals, 216 (50.1%) were females and median age at presentation was 38 months (interquartile range [IQR]: 12–71). 204 (43%) samples were malaria positive. R. felis was found in seven (1.5%) samples from six (1.4%) individuals (three males and three females) out of whom one tested positive twice during the study period. The median age of positive patients was 35 months (IQR: 12–59), with the youngest positive patient 1 month and the oldest 87 months of age (Table 1).

Apart from fever, R. felis-positive patients complained of cough (six out of seven visits) and vomiting (four out of seven visits); however, there were no reports of rash. Malaria coinfection was found in the three oldest positive patients and was absent in patients younger than 36 months. None of the R. felis-positive patients had started antibiotic or antimalarial treatment before presentation and one patient was admitted for treatment. No patient received empirical antimicrobial therapy covering Rickettsia spp. (Table 1).

One patient tested positive for Rickettsia at two out of three visits: Plasmodium falciparum alone was detected on January 25, 2012; R. felis was detected on June 12, 2012 with no concurrent malaria infection identified; at the third presentation on August 17, 2012, a clinical diagnosis of severe malaria was made and tests were positive for both P. falciparum and R. felis. The patient was hospitalized, treated for severe malaria, and discharged 5 days later.

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**R. felis** has been associated with febrile infections and symptoms similar to murine typhus, and was implicated as the causative agent of vesicular fever (‘yaafu’). It occurs worldwide, but data on its distribution in Africa are limited. Here, we report the first detection of *R. felis* in Ghana with 1.5% of febrile pediatric patients being infected. No other rickettsial pathogen was detected. Although infections with the primarily tick-borne spotted fever group rickettsiae appear to be common in West Africa, as suggested by high seroprevalences in Côte d’Ivoire (35%) and Burkina Faso (36%), *R. felis* as a member of the transitional group rickettsiae has only been detected in West Africans from the Sahel-zone countries of Senegal and Mali, where up to 24% of febrile patients were PCR positive.

Malaria coinfection was present in three out of seven *R. felis*-positive patients, and all coinfected patients were older than 36 months. Although these observations need to be interpreted with care, they are consistent with similar findings from Senegal, where coinfection was commonly observed and mostly occurred in older children. Similar age and seasonality patterns of infection, along with the recently reported potential of *Anopheles gambiae* mosquitoes to transmit *R. felis*, have given rise to a new hypothesis on possible common transmission routes of *R. felis* and malaria.

The clinical significance of *R. felis* infection and malaria—*R. felis* coinfection has been controversially discussed. In our study, all patients were febrile, but additional symptoms were nonspecific. No rash was found, which is consistent with other reports from Africa. Remarkably, some authors have detected *R. felis* DNA in blood samples of afebrile individuals, albeit at lower percentages than in febrile patients, thus challenging its role as an obligate pathogen. None of our *R. felis*-positive patients received empiric antimicrobial treatment covering *Rickettsia* spp. and the course of disease could not be monitored as patients were treated on an outpatient basis. Our study design did not allow the definitive determination of *R. felis* as the disease-causing agent. It also remains unclear whether a coinfection with malaria alleviated or aggravated the course of disease.

The significance of repeated detection of *R. felis*, as seen in one of our patients and also observed in other studies, is subject to ongoing discussion and may be explained either by persistence or reinfection. The detection of *R. felis* in afebrile individuals has furthermore led to the hypothesis that humans could be a natural reservoir of *R. felis*. However, as *R. felis* DNA has also been detected on the skin of healthy Senegalese villagers and in the feces of several arthropod vectors such as *Ctenocephalides felis* or *Liposcelis bostrychophila*, it is still unclear to which extent these findings may be influenced by skin contamination.

In conclusion, our study is the first report on the detection of *R. felis* in febrile children in Ghana, and thus adds to the growing evidence for a widespread occurrence of *R. felis* in SSA. To better understand the pathogenesis of *R. felis* infections, future studies should longitudinally monitor the presence of *R. felis* DNA and specific antibodies following infection, and use control groups to determine the clinical significance of *R. felis*, both in the absence and presence of malaria coinfection as well as in asymptomatic patients.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Patient sex</th>
<th>Age at presentation (months)</th>
<th>Fever (°C)</th>
<th>Plasmodium falciparum (per μL)</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ♂</td>
<td>1</td>
<td>38.1</td>
<td>0</td>
<td>Cough, vomiting</td>
<td>ACT</td>
</tr>
<tr>
<td>2 ♂</td>
<td>12</td>
<td>39.9</td>
<td>0</td>
<td>Constipation, cough, vomiting</td>
<td>ACT ceftriaxone, cefuroxime</td>
</tr>
<tr>
<td>3 ♀</td>
<td>26</td>
<td>38.2</td>
<td>0</td>
<td>Cough, vomiting</td>
<td>ACT metronidazole</td>
</tr>
<tr>
<td>4 ♀</td>
<td>35</td>
<td>38.4</td>
<td>0</td>
<td>Cough</td>
<td>ACT amoxicillin, cefuroxime</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>38.9</td>
<td>1,083,760</td>
<td>–</td>
<td>Quinine gentamycin, ceftriaxone, metronidazole, cefuroxime</td>
</tr>
<tr>
<td>5 ♂</td>
<td>59</td>
<td>40.2</td>
<td>54,046</td>
<td>Cough, stomach pain</td>
<td>ACT cefuroxime</td>
</tr>
<tr>
<td>6 ♀</td>
<td>87</td>
<td>39.6</td>
<td>173,830</td>
<td>Constipation, cough, vomiting</td>
<td>ACT cefuroxime</td>
</tr>
</tbody>
</table>

ACT = artesimin-based combination therapy.

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