Clinical, Laboratory, and Epidemiologic Features of Murine Typhus in 97 Texas Children

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Objective: To document the clinical, laboratory, and epidemiologic characteristics of pediatric patients with murine typhus.

Design: Pediatric patients were diagnosed using serologic testing, and clinical, laboratory, and epidemiologic data were retrospectively reviewed.

Setting: Of 97 patients, 77 (79%) were identified and treated as inpatients and 20 (21%) were treated as outpatients; most resided in south Texas.

Patients: Between 1979 and 1996, medical records and patient-physician interviews were available for 97 patients aged 16 years and younger with murine typhus.

Main Outcome Measures: The frequency of clinical symptoms and signs, abnormal laboratory findings, epidemiologic findings, and measures of disease severity were determined.

Results: The clinical triad of fever, headache, and rash occurred in only 43 (49%) of 87 pediatric patients throughout the illness. Musculoskeletal symptoms were experienced by 43% of patients, whereas gastrointestinal tract symptoms (nausea, vomiting, anorexia, and diarrhea) occurred in 77%. Systemic involvement was evident by the frequent occurrence of abnormal laboratory findings referable to multiple organ systems, including the liver, kidney, blood, and central nervous system.

Conclusions: Pediatric infection by Rickettsia typhi usually causes mild to moderate systemic illness. In children, the median duration of illness was 12 days (range, 5-29 days), but severe complications were rare. Length of illness was significantly related to the initial diagnosis, whereas the interval to defervescence was related to therapy with a tetracycline or chloramphenicol. Early recognition and treatment is important to prevent prolonged morbidity.

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MURINE TYPHUS is an endemic zoonosis caused by a small obligate intracellular bacterium called Rickettsia typhi that is transmitted by fleas. The disease occurs worldwide, particularly in warm climates with heavy populations of rat or opossum reservoirs and flea vectors. A dramatic reduction in reported cases of murine typhus began in the 1940s, and the current prevalence of the disease is fewer than 100 cases per year. Despite this fact, murine typhus is still the second most frequently reported rickettsial infection in the United States. Murine typhus often goes unrecognized and is perceived as a clinically mild disease. Texas and regions of southern California have the highest prevalence in the United States, but recent epidemiologic studies have stimulated concern that typhus reservoirs and vectors are spreading. Although most patients are adults, children constitute up to 75% of infections in some outbreaks. Despite this situation, studies with large series of pediatric patients with murine typhus are lacking. This study retrospectively reviews the clinical, laboratory, and epidemiologic findings in 97 pediatric patients with murine typhus diagnosed in Texas from 1979 through 1996.

RESULTS

DEMOGRAPHIC AND EPIDEMIOLOGIC FINDINGS

From 1979 through 1996, 501 murine typhus cases were reported in Texas; 97 were pediatric. The median age of pediatric patients was 8 years (range, 5 months to 16 years). There was a near equal sex distribution: 44 girls (45%) and 53 boys (55%). Sixty-three patients (65%) were Hispanic, 30 (31%) were white, and 1 (1%)...
PATIENTS AND METHODS

All pediatric patients (aged ≤16 years) with a serologic diagnosis of murine typhus identified between January 1, 1979, and December 31, 1996, by the Bureau of Laboratories of the Texas Department of Health, Austin, were included. Cases were confirmed by a 4-fold or greater increase in serum antibody titers to typhus group antigen by indirect fluorescent antibody (IFA) testing or by a single high titer of 128 or greater by IFA and a lower titer to spotted fever group (Rickettsia rickettsii) antigen than to typhus group antigen by IFA. Patient IFA titers to R. typhi greater than 2048 were recorded as 2048 because not all patients’ serum samples were titrated to an end point.

Clinical and epidemiologic data were collected from patient-physician interviews at the time of illness or by retrospective review of medical records. Information for all 97 hospitalized patients or outpatient patients was recorded on standardized Texas Department of Health surveillance forms. Demographic features and vector exposure were documented for all patients. Signs and symptoms were noted as present or absent. Not all data were available for all patients; thus, denominators used for various calculations differ. For laboratory data, each result was classified as within or outside the reference range by standard criteria. Antirickettsial therapy was noted, and response to treatment was determined.

Disease severity was estimated by 3 measurements: length of febrile illness; length of hospitalization; and semiquantitative summation of the number of occurrences of clinical signs and symptoms or the presence of radiographic evidence of pneumonitis, weighting neurologic signs and pneumonitis 3 times more than other findings. Correlation analysis with linear regression was used to determine statistically significant relations between laboratory variables and length of illness, hospitalization, and number of clinical signs. Other historical, clinical, epidemiologic, and laboratory variables were studied for significant relations by correlation analyses, χ² tests, and t tests.

was black. Disease onset described in 42 patients was subjectively characterized as extremely abrupt in 14 (33%), moderately abrupt in 16 (38%), and gradual in 12 (29%).

Flea bites were reported in 23 (34%) of 68 patients at presentation, and flea exposure, defined as close patient-flea contact in flea-infested areas or in areas where animal reservoirs are found (rats, cats, or opossums), was noted for 45 (83%) of 53 patients. Of those with flea exposure, 23 (53%) reported a flea bite; no information about flea bites was available in 3 flea-exposed patients. Twenty-eight (52%) of 54 patients for whom month of illness was provided were ill during the late spring and early summer months: 9 in May (17%), 11 in June (20%), and 8 in July (15%). However, 26 patients (48%) were ill in the remaining months, including fall and winter.

CLINICAL MANIFESTATIONS

Signs and symptoms recorded in patients during their illness are summarized in Table 1. The typical manifestations of rickettsial disease, fever and headache, were common (96 [100%] of 96 patients and 67 [76%] of 88 patients, respectively) and occurred early in the illness at the time of presentation (between days 1 and 2 of illness). A rash was noted for 59 (63%) of 94 patients at some point during the illness (median of 6 days after onset). The triad of fever, headache, and rash was present in 43 (49%) of 87 patients during the illness; however, 83 (90%) of 92 patients exhibited 2 of these signs and 11 (13%) of 87 manifested fever only. Only 14% (5/35) of patients for whom these intervals were available had this clinical triad within the first 3 days of illness. Table 2 lists rash qualities and their frequency. In 46 patients for whom the date of rash onset was recorded, the rash occurred a median of 6.5 days after onset of illness.

Although fever, headache, or both were frequent at presentation, these manifestations were reported in only
All laboratory tests were performed variably among the patients (Table 3). Relevant findings included leukopenia in 37% (25/68) of patients, absolute neutropenia in 68% (39/57), and absolute lymphopenia in 51% (29/57); differential leukocyte counts showed a left shift for 40% (77) of 52 patients tested. Of 26 patients tested, 21% had high erythrocyte sedimentation rates. Significant abnormalities in serum electrolyte values in 43 patients tested included hyporenaemia in 25 (58%) and hypokalemia in 9 (21%). Liver function tests were infrequently performed but frequently had abnormal findings. Serum urea nitrogen level was elevated in only 1 patient; however, serum urea nitrogen–creatinine ratios were elevated (≥20) in 6 (21%) of 29 patients tested. No evidence of renal tubular or parenchymal disease was detected in 49 patients who underwent urinalysis.

The IFA titers were available for 85 patients and date of serologic test was available for 84 patients. The first serum sample for diagnostic confirmation was usually obtained within 3 weeks after onset of illness (median, day 17). The Figure shows the mean titers of R typhi antibodies and the cumulative percentage of patients with serologic confirmation of infection by time after onset of illness. Diagnostic levels of antibodies were detected by 7 days in 13 patients (15%), by 14 days in 52 (62%), by 28 days in 72 (86%), and thereafter in all.

**LABORATORY TESTS**

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Mean titers of Rickettsia typhi antibodies and the percentage of positive serum samples in 84 children with murine typhus vs time after onset of illness. (REPRINTED) ARCH PEDIATR ADOLESC MED/VOL 155, MAR 2001 WWW.ARCHPEDIATRICS.COM

**THERAPY**

Treatment data were available for 93 patients. Antibiotics were used in 89 patients (96%). A tetracycline or chloramphenicol was used in 79 patients (89%): 64 received a tetracycline, 13 received chloramphenicol, and 2 received both. Ten patients received alternative antimicrobial agents.

**SEVERITY**

The median interval to defervescence after tetracycline therapy was 2 days (range, 0–6 days) and after chloramphenicol therapy was 2.5 days (range, 0–11 days) (P = .28). For other antimicrobial agents, the median interval was 6 days (range, 1–14 days; P = .003). At least 56 patients (58%) were hospitalized, and the median hospital stay was 6 days (longest, 21 days). The duration of hospitalization was shorter only for patients who received tetracycline or chloramphenicol treatment vs other antibiotics (median, 6 days; P = .09). Length of hospitalization was longer for tetracycline-treated patients vs those taking other antibiotics (5 vs 6 days; P = .049). Length of hospitalization was longer for tetracycline-treated patients vs those taking other antibiotics (5 vs 6 days; P = .049).

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**Table 3. Laboratory Findings in Pediatric Patients With Murine Typhus**

<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>Patients, No. (%)†</th>
<th>Laboratory Value, Mean (Range)</th>
<th>Reference Cutoff Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest leukocyte count, WBC ×10⁹/L</td>
<td>1/68 (1)</td>
<td>7.7 (2.0-22.1)</td>
<td>Age dependent</td>
</tr>
<tr>
<td>Lowest leukocyte count, WBC ×10⁹/L</td>
<td>25/68 (37)</td>
<td>5.9 (1.6-15.9)</td>
<td>Age dependent</td>
</tr>
<tr>
<td>Highest left shift, % bands</td>
<td>40/52 (77)</td>
<td>16 (1-56)</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Lowest platelet count (×10⁹), platelets/L</td>
<td>23/53 (43)</td>
<td>189 (30-520)</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Lowest hemoglobin</td>
<td>40/58 (69)</td>
<td>0.69 (0.22-0.41)</td>
<td>&lt;0.35</td>
</tr>
<tr>
<td>Lowest serum sodium level, mmol/L</td>
<td>25/43 (58)</td>
<td>136 (128-145)</td>
<td>&lt;138</td>
</tr>
<tr>
<td>Lowest serum potassium level, mmol/L</td>
<td>9/43 (21)</td>
<td>3.8 (2.8-4.7)</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td>Highest SUN level, mmol/L [mg/dL]</td>
<td>1/37 (3)</td>
<td>3.6 [10] (1.1-11 [3-32])</td>
<td>&gt;6.4 [&gt;18]</td>
</tr>
<tr>
<td>Highest serum creatinine level, µmol/L [mg/dL]</td>
<td>0/32</td>
<td>53 [17-97] [0.2-1.1]</td>
<td>&gt;106 [&gt;12]</td>
</tr>
<tr>
<td>Highest SUN-creatinine ratio</td>
<td>6/29 (21)</td>
<td>14.0 (7.5-40.0)</td>
<td>&gt;20.0</td>
</tr>
<tr>
<td>Highest lactate dehydrogenase level, U/L</td>
<td>20/20 (100)</td>
<td>420 (207-642)</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Highest serum aspartate aminotransferase level, U/L</td>
<td>31/38 (82)</td>
<td>97 (29-530)</td>
<td>&gt;45</td>
</tr>
<tr>
<td>Highest serum alanine aminotransferase level, U/L</td>
<td>13/34 (38)</td>
<td>64 (14-243)</td>
<td>&gt;55</td>
</tr>
<tr>
<td>Highest total bilirubin level, µmol/L [mg/dL]</td>
<td>3/36 (8)</td>
<td>10 [0.6] (2-29 [0.1-1.7])</td>
<td>&gt;17 [&gt;1]</td>
</tr>
<tr>
<td>Lowest serum calcium level, mmol/L [mg/dL]</td>
<td>34/39 (87)</td>
<td>33 (18-45)</td>
<td>&lt;1.2</td>
</tr>
<tr>
<td>Lowest serum alanine aminotransferase level, U/L</td>
<td>3/34 (9)</td>
<td>33 (18-45)</td>
<td>&lt;1.2</td>
</tr>
<tr>
<td>Lowest serum calcium level, mmol/L [mg/dL]</td>
<td>3/39 (10)</td>
<td>2.2 [8.8] (1.9-2.5 [7.6-10])</td>
<td>&lt;2.0 [&lt;8.0]</td>
</tr>
</tbody>
</table>

* WBC indicates white blood cells; SUN, serum urea nitrogen.
† Represents the number of patients for whom the highest or lowest specific laboratory finding noted during the clinical evaluation was above (for highest values) or below (for lowest values) the reference cutoff value.
febrile illness was 5 to 29 days (median, 12 days). Although the illness lasted longer in patients not treated with a tetracycline or chloramphenicol (median, 11.0 vs 11.5 days), the difference was not significant (P = .22). However, patients with an initial diagnosis of murine typhus had a significantly shorter illness duration (median, 8 vs 12 days; P = .002). Length of illness was not different between patients with or without rash (median, 11 days); however, the presence of a rash was associated with the initial diagnosis of murine typhus (P < .02, χ² test). No consistent association of laboratory test results with all 3 measures of severity was identified.

INITIAL DIAGNOSIS

Only 32 (34%) of 95 patients were diagnosed initially as having murine typhus. Twenty-four (25%) were diagnosed as having fever of undetermined origin. The remainder of diagnoses reflected individual symptoms and signs typically referable to specific organ systems. Flea bites and exposure were more frequent in patients with murine typhus as an initial diagnosis (11 of 27 vs 12 of 41 and 26 of 27 vs 19 of 26 patients, respectively), but the differences were not statistically significant (P = .15 and .07, respectively, χ² test). Rash was present in 81% of patients (25/31) initially diagnosed as having murine typhus and in only 34 (36%) of the 61 patients who did not receive this initial diagnosis (P < .02, χ² test), and thus this finding was often used as the primary basis for clinical diagnosis. When the triad of fever, headache, and rash was detected at any time during the illness, the initial diagnosis of murine typhus was rendered 47% (20 of 43 patients) of the time, and the triad was more frequent in patients with an initial diagnosis of murine typhus than in those with other initial diagnoses (P = .01). The day of rash detection apparently did not affect the initial diagnosis (5.6 days with rash vs 5.4 days without rash; P = .43). Only 3 (9%) of 32 patients initially diagnosed as having murine typhus were aged 4 years or younger compared with 13 (21%) of 63 with other initial diagnoses (P = .04).

COMMENT

Murine typhus, first recognized as a distinct entity in 1926, remains a major health risk in developing nations and continues to occur with high prevalence in parts of Texas and southern California. Although it is largely perceived as clinically mild, up to 10% of adults with murine typhus require intensive care, and mortality has approached 4%. Most documented cases of murine typhus in the United States are in adults; however, children can make up 73% of cases in other areas of the world. Despite these data, pediatric illness with murine typhus has been particularly neglected. The prevalence of murine typhus in southern and central Texas gave us the opportunity to study this underrecognized pediatric infection. Aside from the higher rate of headache reported in children aged 5 years or older, no other specific finding was significantly associated with age. Moreover, these data indicate that very young children are equally susceptible to *R typhi* infection but are not more severely affected.

This case series analyzed pediatric patients cared for in a primary care setting, either as hospital inpatients or as outpatients, and displaying varying illness severity. Unlike studies of adult populations, our study showed a near equal sex distribution, possibly because of parental initiative or equivalent exposure of children of both sexes. The demographic data indicate that 63 patients (65%) were Hispanic, and the overall distribution approximates the ethnic distribution of south Texas. Exposure to the vector is necessary for inoculation of the rickettsia; however, only 23 (34%) of 68 patients reported a flea bite, and of 42 patients (89%) for whom flea exposure was reported, 23 (55%) also reported flea bite. Thus, the lack of flea bite history should not exclude murine typhus, but its identification can be an important clue because it was present in 26 patients (96%) initially diagnosed with murine typhus.

The triad of fever, headache, and rash has historically been used as a clinical diagnostic tool in rickettsial disease, including murine typhus. Although all 3 of these symptoms and signs were frequent in our patients, only 43 (49%) of 87 patients displayed all 3 simultaneously. These data illustrate the inconsistent usefulness and unreliability of this triad of clinical findings in the diagnosis of murine typhus. Also, rash appeared an average of 5 days after onset of symptoms and was thus an unreliable early indicator of murine typhus. Macular and maculopapular rashes were frequent; however, only 10% of patients had petechiae (5 of 48 with rash description). Unlike findings noted in previous studies of pediatric murine typhus, headache was frequently noted, especially in older children.

Gastrointestinal tract symptoms were also frequent and might confound diagnosis, leading to inappropriate surgical intervention. As opposed to another study, hepatomegaly was noted in only 3 (4%) of 73 patients, potentially explained by the early treatment in patients in Texas or by the presence of other infections in more tropical settings. The presence of elevated serum activities of transaminases, lactate dehydrogenase, and alkaline phosphatase indicate frequent but mild liver injury possibly due to hepatocyte and biliary injury adjacent to inflamed microvasculature. Despite this, mild hyperbilirubinemia was infrequent and jaundice was absent. Similarly, *R typhi* systemic vasculitis allows extravasation of protein and electrolytes, consistent with the hypoproteinemia and hypoalbuminemia that were frequently observed. Direct renal injury is not a frequent component of pediatric murine typhus.

Some simple laboratory tests might help suggest the diagnosis in the correct clinical setting. Most patients had leukocyte counts within the reference ranges, consistent with previous findings in adults. Because a systemic infection is usually associated with leukocytosis, the presence of leukopenia or a normal leukocyte count in an ill child, especially linked with a left shift, is a helpful finding. Moreover, the presence of leukopenia or thrombocytopenia in a febrile patient also with evidence of mild hepatic injury and flea exposure would suggest the possibility of murine typhus or other rickettsial infection.

Complications of murine typhus are infrequent in children. Central nervous system manifestations were relatively few in this study, but 6 patients experienced...
ataxia and stupor, consistent with previous clinical descriptions. In contrast, neurologic findings were reported in 15% to 45% of adult patients. The reason for the discrepancy between children and adults is unclear but perhaps might be due to early recognition and therapy in children or intrinsic resistance of children to the infection. In addition to central nervous system abnormalities, 10 patients had increased densities on chest radiographs. One patient required intensive care, another had a relapse after initial therapy, and a third had an appendectomy. There were no other significant complications and no fatalities, although a case fatality rate of 1% to 4% is noted in adults. Regardless, our results indicate that a substantial proportion of patients had severe illness characterized by a febrile interval of 14 days or more (23%; 19 of 81 patients) or hospitalization of 7 days or more (36%; 20 of 56 patients). Thus, murine typhus has the potential to cause significant and prolonged morbidity in children, with undefined long-term sequelae. When murine typhus is suspected, treatment and confirmation should not be delayed. It is well documented that tetracycline and chloramphenicol are effective agents to which R typhi–infected patients respond promptly. In our study, the median 2-day interval until defervescence after therapy supports the effectiveness of this regimen for murine typhus.

Murine typhus is infrequently suspected in pediatric patients; diagnoses other than murine typhus were initially rendered for most. Because patients present with single-system complaints, the initial diagnosis is frequently erroneous. However, murine typhus was the single most common initial diagnosis probably because of physicians having a high index of suspicion in an endemic area. Although the increased early recognition demonstrated here is encouraging compared with previous studies, the data suggest an overreliance on the detection of rash or the clinical triad of fever, headache, and rash before diagnosis and specific therapy. This is important because early diagnosis and treatment leads to shorter illness and hospitalization.

Nationwide, there has been increased concern about the emergence of tickborne diseases such as Lyme disease, ehrlichioses, and Rocky Mountain spotted fever. In Texas, the potential for reemergence and more widespread occurrence of murine typhus might be even greater than for these tickborne infections. From 1995 through 1998, 211 cases of murine typhus were reported in Texas, whereas only 18 cases of Rocky Mountain spotted fever and 6 cases of ehrlichiosis were reported. The potential for reemergence of this fleaborne disease might also be present in other states. Early recognition of emerging and reemerging infections depends on the ability of clinicians to identify specific clinical and laboratory findings characteristic of the disease. The findings in this study provide increased knowledge of such manifestations in murine typhus, increasing the ability to detect and promptly respond to this poorly recognized endemic zoonosis.

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