Human Monocytic Ehrlichiosis in Children

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ABSTRACT. ***Background.*** **Much of what is known about human monocytic ehrlichiosis (HME) is based upon studies with adult patients.**

Purpose. **To review our experience with HME to better understand the epidemiology, clinical manifestations, and outcome of this disease in children.**

Methods. **Demographic, clinical, and laboratory data were gathered after review of the medical records of patients identified with HME.**

Results. **Twelve patients with an median age of 7.4 years (range, 7 months to 13.7 years) were identified with HME; 10 were white, 7 were male, and 10 were from hometowns of <800 people. Eight patients presented from May through July, and 8 had a history of tick bites. Symptoms demonstrated by the patients during their illness included fever (100%), rash (67%), myalgias (58%), and vomiting, diarrhea, and headache (25%). On presentation, patients demonstrated thrombocytopenia (92%), elevated liver function tests (91%), lymphopenia (75%), hyponatremia (67%), leukopenia (58%), and anemia (42%) on the initial laboratory examination. Four patients presented in shock and 3 required blood pressure support and mechanical ventilation for a median of 10 days (8 to 37 days). These complicated patients required longer hospitalization (19.5 days vs 5.5 days) and attained higher blood urea nitrogen levels (42.5 mg/dL vs 10 mg/dL) than the patients not presenting with shock. Morbidity associated with HME patients included a decrease in cognitive and neurologic performance.**

Conclusions. **More information and long-term follow-up is required to understand the full spectrum of disease and morbidity associated with HME in children.** ***Pediatrics*** **1997;100(1). URL: http://www.pediatrics.org/cgi/content/full/100/1/e10;** ***erlichiosis, children, rickettsia, ticks.***

ABBREVIATIONS. HME, human monocytic ehrlichiosis; RMSF, Rocky Mountain spotted fever.

In the 10 years that human monocytic ehrlichiosis (HME) has been recognized in the United States, much of our knowledge concerning the clinical presentation and outcome of this illness has been obtained from experience with adult patients.[1,2] This is because only approximately 10% of the patients described to date have been children.[3] As our knowledge of HME increases, it is imperative that we continue to gather data which will allow us to better understand the epidemiology and natural history, the clinical manifestations and the role of therapy, the prognostic indicators for outcome, and the long-term morbidity and mortality of this illness. The purpose of this study was to review our experience with HME to gain a better understanding of the features of ehrlichiosis in children.

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MATERIAL AND METHODS

A retrospective review of all medical and laboratory records from Arkansas Children's Hospital from 1990 to 1996 were reviewed in an attempt to identify all patients infected with *Ehrlichia chaffeensis*. Patients were considered to have a diagnosis of HME if the patient had a clinically compatible history with a minimum titer to *E chaffeensis* of ≥1:64 or a fourfold or greater change in antibody titers from acute and convalescent sera using indirect fluorescent antibody testing.[4] Once the patients were identified, the medical records were reviewed to gather demographic data as well as data concerning tick-bite history, dog ownership, number of symptomatic days before seeking medical attention and before antirickettsial therapy was started, chief complaint, hospital course, antimicrobial agents before antirickettsial therapy, antirickettsial agent used, length of therapy, days to fever defervescence, physical examination abnormalities, laboratory examinations, morbidity, and mortality. Patients were identified as complicated if they required intensive care therapy, pharmacologic blood pressure support, or mechanical ventilation. Data on Rocky Mountain spotted fever (RMSF), tularemia, and Lyme disease reported to the Arkansas Department of Health from 1994 to 1996 were obtained for comparison. These limited dates were chosen because ehrlichiosis did not become a reportable disease in Arkansas until January 1994. Differences between groups classified as complicated or uncomplicated were compared using the Student's *t* test (two-tailed).

RESULTS

Twelve patients were identified as having a diagnosis of HME. Fifty-eight percent of the patients were male, 83% were white, and 17% were African-American; the median age was 7.4 years (range, 7 months to 13.7 years). Eighty-three percent of patients were from rural areas (<800 population) and the infections occurred in May (n = 7), June (n = 3), October (n = 1), and November (n = 1). Ten patients were previously healthy although one patient had undergone a renal transplant from a living related donor 6 weeks before this illness and a second patient suffered from sickle β-thalassemia. Data obtained from the Arkansas Department of Health revealed that cases of RMSF (n = 70), tularemia (n = 64), Lyme disease (n = 50), and ehrlichiosis (n = 33) were all reported from 1994 to 1996. Children <15 years of age were identified in 29% of the cases of RMSF, 48% of the cases of tularemia, 12% of the cases of Lyme disease, and 21% of the cases of ehrlichia during this time period.

Eighty-nine percent of our patients admitted to a

history of tick bite and 50% were dog owners. The symptoms at presentation are outlined in Table 1. Patients admitted to having symptoms for a median of 2 days (range, 1 to 9 days) before seeking medical evaluation. The median temperature upon presentation was 39.5°C (range, 38.4°C to 40.8°C). Findings on physical examination are outlined in Table 2. The hematologic and blood chemistry abnormalities upon hospitalization are outlined in Table 3. Seven of these patients demonstrated thrombocytopenia, elevated liver function tests, and lymphopenia at the time of hospitalization. All 12 patients had serologic confirmation of HME with 58% diagnosed without the use of convalescent titers (Table 4). The renal transplant patient had morulae demonstrated in cytoplasma of the monocytes on examination of the bone marrow and was the only patient in which this procedure was done. No morulae were visualized on the peripheral smear of any patients.

All patients were treated with doxycycline (4 mg/kg/day given twice daily either intravenously or orally for 10 to 14 days), and the median time to temperature defervescence was 48 hours (range, 24 to 480 hours). Sixty-seven percent of patients had received two or more antimicrobial agents before starting doxycycline. Eight patients had uneventful hospitalizations, whereas four had a complicated course and were admitted to the intensive care unit (Table 5). Three of these patients required intubation and pharmacologic blood pressure support with a median number of 10 days (range, 8 to 37 days) for intubation. The fourth patient required volume resuscitation alone for hypotension. Two of the complicated patients underwent a lumbar puncture in their initial evaluation because each presented with hypotension and petechiae (patients 1, 4; Table 5). Both patients had an elevated cerebrospinal white blood cell count (133/mm^3 and 109/mm^3) and protein (74 mg/dL and 103 mg/dL) with negative bacterial cultures from the blood and spinal fluid. Two of the complicated patients included the only two African-American patients. There was no difference between the complicated and uncomplicated groups concerning the number of days of symptoms before seeking medical attention/receiving antirickettsial therapy, or the amount of bone marrow suppression demonstrated during the course of their illness. The median number of days of hospitalization (19.5 days vs 5.5 days; $P < .05$) and the median blood urea nitrogen levels (42.5 mg/dL vs 10 mg/dL; $P < .05$) were different in complicated cases compared with uncomplicated cases.

TABLE 1. Symptoms of Patients at Hospital Admission

Symptom	No. (%)
Fever	12 (100)
Rash	8 (67)
Myalgia	7 (58)
Headache	3 (25)
Vomiting	3 (25)
Diarrhea	3 (25)
Puffy eyes	3 (25)
Upper respiratory infection	2 (17)
Night sweats	2 (17)
Abdominal pain	2 (17)
Productive cough	2 (17)
Irritability	1 (8)
Combative	1 (8)
Weight loss	1 (8)

TABLE 2. Findings on Physical Examination at Hospital Admission

Finding	No. (%)
Rash	8 (67)*
Murmur	4 (33)†
Hepatosplenomegaly	3 (25)
Dehydration/poor perfusion	3 (25)
Others‡	

* Macular alone (1), macular-papular (1), petechiae (2), and combination of any (4).
† II/VI systolic ejection murmur best audible at the left lower sternal border.
‡ Combative/irritable (2), yellow exudate in nasopharynx, crackles in left lower lobe, wheezing bilaterally, distended abdomen with diffuse tenderness, oral ulcer, and inguinal adenopathy.

TABLE 3. Hematologic and Blood Chemistry Abnormalities Upon Hospital Admission

Findings	No. (%)*
Thrombocytopenia (<150 000/mm^3)	11 (92)
AST (>55 U/L)	10 (91)†
Lymphopenia (<1500/mm^3)	9 (75)
ALT (>55 U/L)	8 (67)
Hyponatremia	8 (67)
(<135 mEq/L)	5
(<130 mEq/L)	3
Leukopenia (<4000/mm^3)	7 (58)
Anemia (Hct < 30%)	5 (42)
Cr (>1.0 mg/dL)	2 (17)
BUN (>36 mg/dL)	2 (17)

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotranferase; Cr, creatinine; BUN, blood urea nitrogen.
* Numbers in parenthesis represent the percentage of patients with the abnormal laboratory values.
† Available only on 11 patients.

Long-term follow-up at 1 year of a 7-year-old female (patient 6; Table 4) revealed a decrease in school performance based upon her grades, a decrease in her ability to read aloud, and a noticeable worsening in her handwriting and fine-motor skills. Neuropsychologic testing revealed her to be within the average range on the Wide Range Achievement Test-3 and on the Clinical Evaluation of Language Fundamentals—Third Edition. She was found to have a relative weakness in formulating complete sentences and immediate recall of information. Her speech production skills, hearing, and vision were considered normal. A 7-month-old who demonstrated diffuse cerebral atrophy on computed tomography and magnetic resonance imaging at discharge is developmentally appropriate at 2 years of age. An 11-year-old male demonstrated a left upper extremity weakness with a bilateral foot drop and a speech impediment that required prolonged hospitalization and rehabilitation. The bilateral foot drop was thought to be from the development of bilateral sciatic nerve palsies from prolonged hospitalization. Upon discharge he was noted to have difficulty with abstract reasoning and recent memory. He also had problems

TABLE 4. Reciprocal Antibody Titers to *Ehrlichia*

Patient	Acute		Convalescent	
	IgM	IgG	IgM	IgG
1	160	256	ND	ND
2	<16	<16	≥320	≥1024
3	≥320	256	ND	ND
4	≥320	≥1024	ND	ND
5	≥320	≥1024	ND	ND
6	ND	160	ND	5120
7	<16	<16	20	256
8	ND	<16	ND	256
9	20	256	ND	ND
10	<16	<16	<16	64*
11	80	≥1024	ND	ND
12	80	≥1024	ND	ND

Abbreviations: IgM, immunoglobulin M; IgG, immunoglobulin G; ND, not done.
* Convalescent titer was drawn 3 days after the acute titer. No other follow-up serology was obtained.

TABLE 5. Complications and Outcome of Complicated Ehrlichiosis Cases

Patient	Complications	Outcome
1	Hypotension, hypoxia, cerebral atrophy	Intermittent wheezing, developmentally normal at 2 years of age
2	Hypotension, ARDS	Hypertension
3	Hypotension, DIC, encephalitis, MOSF, dialysis	Speech impediment, bilateral foot drop, hypertension
4	Hypotension, tachycardia	Normal

Abbreviations: ARDS, adult respiratory distress syndrome; DIC, disseminated intravacular coagulation; MOSF, multiorgan system failure.

with carrying out two-step commands and in complex problem solving. Follow-up at 1 year postillness demonstrated that he had returned to school and was performing well. His speech was understandable to others. Although his bilateral foot drop had improved, he still had some difficulty picking his feet up, which has led to frequent tripping. The last two of these patients were considered complicated based upon their presentation for medical therapy (Table 5).

DISCUSSION

HME is not as frequently reported in the children of Arkansas as the other tick-borne illnesses such as RMSF and tularemia. It is known that the ticks harbor the spotted fever group of rickettsiae (4.8%) more often than *Francisella tularensis* (1.8%), *E chaffeensis* (0.3%), or *Borrelia burgdorferi* (0.1%).[5,6] The low numbers of reported infections in Arkansas may be attributable to the low number of infected ticks or the lack of adequate identification and reporting of this illness. Comparing RMSF, tularemia, and ehrlichiosis, we recognize the fact that reports from our institution comprise approximately 39% of the cases of RMSF, 38% of the cases of tularemia, but all of the ehrlichia cases in children <15 years of age (data not shown). This is not consistent with the other tick-borne illnesses and would support the theory that this disease is either significantly underdiagnosed or underreported in Arkansas.

Our patient population differed from other series of ehrlichiosis in children. Seventeen percent of our patients were African-American and/or had an underlying condition which may have predisposed them to illness.[7–16] Previous reported cases have included only white children. Both patients who were African-American were complicated cases resulting in prolonged mechanical ventilation and hospitalization. Patients with darkly pigmented skin have been recognized to be at risk for more severe disease with other rickettsial diseases (eg, RMSF) although the proposed mechanism for severe disease has been the delayed recognition of the illness secondary to the difficulty in detecting a rash.[17] The delay in recognition of HME may have been more important than the patients' race because both began antirickettsial therapy at 4 or more days after the onset of their symptoms. This delay in therapy is known to have an increased risk of poor outcome in RMSF.[18] Although patients with concomitant ehrlichiosis and significant underlying diseases have been described in adults,[19,20] with the exception of one child with Down syndrome,[7] all the children described previously have been healthy.[7–16] Of the two children with underlying disorders presented in this study, an African-American child with sickle β-thalassemia required mechanical ventilation and prolonged hospitalization with resulting hypertension. The renal transplant patient responded to doxycycline very quickly and recovered without incident.

The presence of a rash was demonstrated in 67% of our patients and was found to occur in 65% of all reported pediatric cases in a recent review.[3] This continues to be noted more commonly in children than in adults, in which the concomitant occurrence of a rash has been described in 36% to 47% of patients.[21,22] The laboratory abnormalities of ehrlichiosis in children are well recognized.[3,23] Based on these data, however, it was of interest to note that a greater percentage of our patients suffered from thrombocytopenia (92% vs 80%), anemia (42% vs 28%), and hyponatremia (67% vs 33%) whereas fewer had leukopenia (58% vs 72%) than had been previously noted.[3] This may be because these previous cumulative data are based upon

laboratory results from only 18 patients and may represent variations as the patient numbers increase.

Mortality from ehrlichiosis gathered mainly from adults is known to occur in <2% of patients with approximately 16% suffering from serious manifestations or clinical complications.[21] Twenty-five percent of our patients had serious manifestations of illness which were not described in the only other series in children of comparable size.[12] In a recent review of life-threatening illness with *Ehrlichia*, 56% of the patients described were <15 years of age.[16] Clinicians, therefore, should consider the diagnosis of ehrlichiosis in patients who present with a culture-negative sepsis syndrome, especially those with a tick-exposure history and/or compatible laboratory manifestations.

There has been little data on the renal morbidity of ehrlichiosis in pediatric patients. Our data demonstrated that patients who attain high blood urea nitrogen levels (excluding the renal transplant patient) have a greater risk for prolonged hospitalization. However, these results should be seen as preliminary because they are based on a small number of patients and similar observations have not been recognized among adult patients. Renal failure is known to occur in approximately 6% of adult patients,[21] but has never been described in children before this report. The development of long-term hypertension in two of our complicated patients is probably attributable to a combination of renal failure and the severity of their illness.

The long-term neurologic morbidity in two of our patients has been demonstrated for pediatric patients with RMSF, but never with ehrlichiosis.[24,25] Long-term neurological sequelae such as paraparesis, peripheral neuropathy, learning, speech, and behavioral disturbances have been documented. These problems usually are encountered in the patients with the more severe forms of RMSF. Only one of our patients with prolonged neurologic sequelae was considered to be a complicated patient. Although his bilateral foot drop might have truly resulted from his prolonged positioning, it is important to emphasize that all patients who experience neurological sequelae with RMSF do not have permanent problems, so the same might be true with ehrlichiosis.[25] The decreased school performance in our 7-year-old child is a little more difficult to understand. She was not recognized to be severely ill, was afebrile within 36 hours of treatment, and was home within 4 days. Even though her psychomotor testing revealed her to be within the normal range, her school teachers and family noted a distinct change in her performance. These data indicate that prolonged neurological complications of ehrlichiosis may occur without the presence of severe disease.

Classic HME in children is becoming easier for clinicians to recognize and treat although RMSF needs to be strongly considered in the differential diagnosis of these patients. Patients with fever, a history of tick bite, and the presence of compatible laboratory abnormalities should alert the physician to the possible diagnosis. The issue of the proper medication for the treatment of HME in children is not as simple. The lack of an understanding about asymptomatic infections and the need for antimicrobial therapy complicates the treatment issues. We chose to treat all patients (regardless of their age) with doxycycline because all were symptomatic and required hospitalization. The choice of doxycycline was based on recent data demonstrating that patients with RMSF who were treated with doxycycline were less likely to die than patients treated with chloramphenicol[18,26] and the knowledge that the staining of the teeth by the tetracyclines seems to be dose related.[27] Questions concerning the efficacy of chloramphenicol in the treatment of HME[21,28] and the lack of a liquid chloramphenicol product in the United States were also important factors in this decision. Further research will be required to adequately address these treatment issues.

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