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Comparative Analysis of Severe Pediatric and Adult Leptospirosis in São Paulo, Brazil

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Abstract. Although leptospirosis may be fatal in childhood, the experience of many clinicians working in disease-endemic areas is that classic Weil's disease and death are less common among pediatric patients. The aim of the study was to ascertain disease spectrum and outcome differences in severe pediatric and adult leptospirosis in a large at-risk population. Epidemiologic, clinical, and laboratory data were obtained on hospitalized cases from São Paulo during 2004–2006. A total of 42 case-patients < 18 years of age and 328 case-patients ≥ 18 years of age were tested during the study. Compared with children, adults had higher rates of jaundice ($P = 0.01$), elevated serum bilirubin levels ($P < 0.01$), oliguria ($P = 0.02$), and elevated creatinine levels ($P = 0.01$) but not for thrombocytopenia or pulmonary involvement. The overall case-fatality rate was 27% (adult) versus 5% (pediatric) ($P < 0.01$). Severe pediatric leptospirosis may be less likely to show all classic features of Weil's disease and may be less fatal than in adults.

INTRODUCTION

Leptospirosis is a globally important zoonosis caused by pathogenic spirochetes of the genus *Leptospira*. Infection results from exposure to the urine of mammalian reservoirs in the setting of flooding after heavy rains, peridomestic contact with rodents and other mammalian reservoirs, occupational (e.g., veterinary) exposures, or selected recreational activities such as rafting or adventure racing.[1,2] Serosurveys in disease-endemic areas have repeatedly shown that infection in children and adults most commonly results in asymptomatic or self-resolving illness.[3] However, the incidence and disease spectrum of pediatric and adult leptospirosis are not well-described in most areas, and precise information on the frequency and types of severe manifestations in sizeable pediatric populations is limited.[4–6]

Experienced clinicians in disease-endemic areas commonly believe that leptospirosis produces milder symptoms among children.[5–7] In adult case series, approximately 5–10% of human infections indicate severe disease, including the classic Weil's syndrome triad of acute renal failure, jaundice, and hemorrhage (with or without severe pulmonary hemorrhage syndrome [SPHS]) and case-fatality rates ranging from 5–15% (Weil's) to ≥ 50% (SPHS).[1,2] The rate of SPHS (and thus the case-fatality rate) may be increasing in urban Brazil and elsewhere in Latin America[8–10]; thus far, most reported SPHS occurs in adults.[9] In São Paulo, Brazil, SPHS is commonly observed among hospitalized persons,[11] and nearly three-fourths (74%) of patients who die have Weil's syndrome and SPHS.[12]

Leptospirosis is highly endemic to São Paulo, Brazil, and is a leading cause of hospital and intensive care unit admission throughout much of the year. Using Municipality of São Paulo leptospirosis data on severe leptospirosis (serologically confirmed data primarily from hospitalized patients), we examined the related hypotheses that severe pediatric leptospirosis is less likely to present with all the classic features of Weil's disease and/or SPHS, and that the case-fatality rate for severe leptospirosis is lower in children.

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METHODS

Surveillance. The study was conducted in collaboration with the Health Coordination Department, Municipality of São Paulo from January 2004 through December 2006 among hospitalized patients with leptospirosis. The study protocol included standardized medical record and patient questionnaires that contained demographic, epidemiologic, clinical, and laboratory information, including necropsy data among fatal cases. Outpatient testing results for leptospirosis were not included in the analysis.

Leptospirosis was defined by a compatible clinical syndrome (any combination of fever, chills, myalgia, jaundice, conjunctival suffusion, renal failure, hemorrhage, or pulmonary failure) and laboratory confirmation with one or more of the following features: 1) positive results for an IgM enzyme-linked immunosorbent assay (PanBio, Windsor, Queenland, Australia and Biomanguinhos, Manguinhos, Brazil); 2) positive results for a microscopic agglutination test (using a panel of 20 serovars) and one acute-phase serum sample titer > 1:800, 3) seroconversion between times of testing acute-phase and convalescent-phase serum samples, 4) a four-fold increase in titers between two examinations, or 5) positive blood cultures. Among fatal cases, an additional criterion included pathologic evidence of leptospirosis at necropsy (when performed) in patients meeting the above criteria. Patients were stratified by age: 0–17 years of age (pediatric) and ≥ 18 years (adult).[12]

Clinical and laboratory definitions. Oliguria was defined as urine output < 0.5 mL/kg/day (pediatric) or < 400 mL/kg/day (adult), and pulmonary involvement was defined as dyspnea, hemoptysis, rales, chest radiographic abnormalities, and/or requirement for mechanical ventilation for adults and pediatric patients. Laboratory results refer to samples collected at the time of admission. Reference values were serum creatinine = 0.7–1.2 mg/dL, total bilirubin = 0.8–1.2 mg/dL, and platelet counts = 150,000–400,000/mm^3. The time (in days) between onset of symptoms and hospitalization was compared between groups. A minimum at least of two normal or abnormal laboratory values was used to define disease status.

Statistical analysis. STATA (Stat Corp., College Station, TX) was used for analysis. Quantitative and qualitative variables were compared by using paired Student's *t*-tests and chi-square tests, respectively. When the frequency of events was < 5 or values did not follow normal distributions, Fisher's Exact and Mann-Whitney tests were used.

TABLE 1
Demographic and clinical features in pediatric and adult groups, São Paulo, Brazil*

Characteristic	Patients < 18 years of age (n = 42)	Patients ≥ 18 years of age (n = 328)	*P*
Age, years	12.5 ± 3.8	40.1 ± 13.8	< 0.01
Deaths	2/42 (5)	87/328 (27)	< 0.01
Jaundice	26/41 (64)	261/318 (82)	< 0.01
Bilirubin level (mg/dL)	5.6 ± 6.8	12.2 ± 11.8	< 0.01
Oliguria	16/41 (39)	190/317 (60)	0.02
Serum creatinine level (mg/dL)	2.4 ± 1.8	3.4 ± 2.4	0.01
Male sex	31/42 (74)	281/328 (86)	0.08
Days of symptoms before admission	4.7 ± 2.6	5.9 ± 4.3	0.07
Pulmonary involvement	13/39 (33)	120/311 (39)	0.64
Mean platelet count/mm^3	110,221 ± 73,342	110,303 ± 114,387	0.99
Serogroup Icterohaemorrhagiae†	21/30 (70)	168/223 (75)	0.53

*Values are mean ± SD or n/N (%).
†As predicted by the highest microscopic agglutination test titer.

RESULTS

During the study period, 90 children and 545 adults were confirmed to have severe leptospirosis by clinical and laboratory criteria. Of these persons, 42 children and 328 adults met the study criteria including adequate documentation of laboratory values needed to define severe disease status. When we compared pediatric and adult leptospirosis, adults exhibited a higher frequency of jaundice (261 of 318 versus 26 of 41; $P = 0.01$) and oliguria (190 of 317 versus 16 of 41; $P = 0.02$). Mean total serum bilirubin and serum creatinine levels were also higher in adults than pediatric groups (12.2 versus 5.6; $P < 0.01$ and 3.4 versus 2.4; $P = 0.001$, respectively). The groups showed no differences with respect to pulmonary involvement. More than three-fourths of patients in pediatric and adult groups were male ($P = 0.08$). The time between onset of symptoms and hospitalization was moderately shorter among pediatric patients (4.7 versus 5.9 days; $P = 0.07$). The case-fatality rate was substantially higher in adults (27%, 87 of 328 than in children (5%, 2 of 42) ($P < 0.01$) (Table 1).

The percentage of patients with each of the well-described features of Weil's disease was analyzed. Children were more frequently hospitalized lacking any features of Weil's syndrome (11 of 42, 26%) than adults (33 of 328, 10%) ($P < 0.01$). The combination of two severe disease manifestations (e.g., oliguria and pulmonary involvement) had similar rates in children (9 of 42, 21%) and adults (93 of 328, 28%) ($P = 0.34$). However, the case-fatality rate was lower in children (1 of 9, 11%) than in adults (55 of 93, 59%) ($P = 0.01$). In analyzing atypical presentations of severe disease among pediatric patients, we observed that oliguria in the absence of jaundice was observed in 5 (12%) of 42 children and in 19 (6%) of 328 (6%) adults ($P = 0.13$). Respiratory failure in the absence of jaundice was observed in 3 (7%) of 42 pediatric patients and 13 (4%) of 328 adult patients ($P = 0.28$).

The frequencies of seroreactivity to serogroup Icetrohaemorrhagiae (on the basis of highest microagglutination test titer) were 21 (70%) of 30 pediatric patients and 168 (75%) of 223 adult patients ($P = 0.53$). No culture isolates were obtained. Risk factors for leptospirosis transmission did not differ between the groups; most patients in both groups had self-reported indirect or direct contact with rodent urine (77% in children and 81% in adults), flooded areas (35% versus 50%), garbage or sewers (30% versus 44%), and nonrodent mammalian carriers (15% in both groups). The spatial distribution of patient homes was mapped by using a geographic information system across São Paulo and was similar for both groups.

DISCUSSION

Our study found that a substantial proportion of hospitalized children with leptospirosis had fewer of the classic features of Weil's disease and lower case fatality rates than adults. In a previous series of 52 children (0–12 years of age) with serologic confirmation of leptospirosis in Rio de Janeiro, less than half (44%) had evidence of acute infection with fever and other classic symptoms and signs.[13] In Salvador, another large urban Brazilian center, a comparison between 1,016 hospitalized patients < 19 and ≥ 19 years of age also reported lower rates of jaundice among children and adults (80% versus 93%, respectively) and a lower case-fatality rate in pediatric patients (3% versus 16%, respectively).[14]

Although severe disease and death caused by leptospirosis may occur in pediatric age groups and there may be significant disease overlap with the spectrum seen in adults, the frequency of several classic severe disease manifestations and overall case-fatality rates were significantly lower among children in this study and among patients with severe renal and pulmonary disease. These differences did not appear related to differences in seroreactivity to leptospiral serogroups; the latter was similar in both groups. It is possible that clinicians have a lower threshold to admit children with suspected or confirmed leptospirosis to the hospital ($P = 0.07$ for comparing onset of symptoms to hospitalization). Regardless, these observations may guide clinicians toward increased clinical suspicion of pediatric leptospirosis because typical features of Weil's disease may be absent in more 25% of all severe cases, and the classic disease triad may be incomplete in most patients. Investigators seeking insights into the pathogenesis of severe leptospirosis should further examine the physiologic and/or immunologic factors associated with improved pediatric outcomes.

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