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Israeli rickettsial spotted fever in children

A review of 54 cases

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Summary

We observed and recorded clinical and laboratory data from 54 children with fever and a maculo-papular rash admitted to Soroka Medical Center, Beersheva, Israel suffering from serologically confirmed rickettsial spotted fever. The rash generally began on the palms and soles and extended centripetally to the torso. Other clinical findings included myalgia, headache, hepatomegaly, and splenomegaly. None had a “tache noire”. A left shift in the white cells, leucopenia, thrombocytopenia, hyponatraemia and impaired liver function tests were common laboratory abnormalities. All recovered following oral doxycycline therapy. Serious sequelae such as myocarditis, encephalitis, and disseminated intravascular coagulation, as reported in Rocky Mountain spotted fever, did not occur.

Key words: Israeli spotted fever; rickettsia; rickettsial spotted fever.

Introduction

Spotted fever is the name given to a variety of tick-borne rickettsial diseases endemic to many regions of the world. In Israel spotted fever is different from Boutonneuse fever as reported in other countries of the Mediterranean basin in that a “tache noire” or eschar is seldom if ever seen (Goldwasser et al., 1974; Gross et al., 1982). In addition, strains of spotted fever isolated in Israel have been shown, by the immunofluorescent antibody method, to be different, from other members of the spotted fever group rickettsiae (Goldwasser et al., 1974).

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A controlled clinical trial was done in which the efficacy of doxycycline was evaluated in treating Israeli spotted fever in children (Yagupsky P., Gross E. M., Alkan M., and Bearman J. E., in preparation). During this trial, clinical and laboratory findings of patients suffering from spotted fever were noted. This is a report on these observations in serologically confirmed cases.

Patients and Methods

Primary care paediatricians in southern Israel were requested to refer all cases of suspected spotted fever presenting with a fever and a maculo-papular rash including the palms and soles to Soroka Medical Center to take part in the clinical trial. All cases were hospitalized for one week. They were treated with oral doxycycline. A complete blood count, erythrocyte sedimentation rate (ESR), and blood chemistry, including liver function tests, glucose, and electrolytes, were done.

Acute and convalescent sera were drawn for examination for specific antibodies to spotted fever group rickettsiae according to the immunofluorescent antibody method which has been described elsewhere (Goldwasser and Shepard, 1959) and is briefly summarized. Spotted fever group rickettsiae were grown in embryonated hens' eggs. Whole rickettsial antigen was prepared by differential centrifugation and ether extraction. For the examination of the sera for specific antibodies, the antigen was diluted in 1% crude yolk sac suspension. Drops of antigen (approximately 1 μ l each) were applied to clean microscope slides, air dried, and fixed in acetone. The sera were diluted in 20% normal yolk sac extract to a dilution of 1:40. The sera in question were overlayed on the spotted fever antigens at the 1:40 dilution. The overlayed antigens were incubated in a wet chamber for 30 min at 37°C. The slides were washed in phosphate-buffered saline and air dried. The complex was then overlayed with a commercially prepared fluorescent-labeled, anti-human IgG or IgM solution, reincubated, washed, and air dried as described above. For each set of slides prepared at one time, a known positive and negative control serum was processed with the sera in question. The fluorescent staining was graded from 4+ (brilliant, as in the case of the positive control), to – (no staining, as in the case of the negative control). Test sera were considered positive only if they were $\geq 2+$.

Patients who failed to demonstrate specific IgM antibodies at the end of a week of hospitalization were retested up to three months after the onset of illness in order to check for the appearance of these or specific IgG antibodies. Patients failing to demonstrate specific anti-spotted fever group antibodies were not included in the study.

Results

Fifty-four children ill with serologically proven spotted fever were admitted to Soroka Medical Center (from June to December inclusive during a three year period). Thirty-nine (72%) were male. Ages ranged from four months to 13 years. Forty (74%) were younger than nine years of age (Table 1).

In the four cases from whom a history of a tick bite could be elicited, the incubation period was seven or eight days, the time from the presumed infecting bite until the onset of first symptoms.

The initial symptom of the disease noted by patients or family members was a rise in temperature. The rash was noted as early as the same day as the onset of fever and as late as seven days following the onset of fever, with 27 (50%) of the patients demonstrating a rash between days three and five inclusive following onset of fever. In general, the rash began on the hands and feet and extended centripetally. It consisted of 2–5 mm diameter deep red, non confluent

Table 1. Age and sex distribution of 54 cases of Israeli spotted fever

Age (years)	Sex	
	Male	Female
0-<2	5	2
2-<4	9	2
4-<6	9	5
6-<8	7	1
8-<10	5	1
10-<12	3	4
12-<14	1	
Total	39	15

Table 2. Symptoms and signs in 54 children with Israeli spotted fever

	Number	Percentage
<i>Symptoms</i>		
Fever	54	100
Rash	54	100
Myalgia	18	33
Vomiting	17	31
Headache	12	22
Arthralgia	7	13
Diarrhea	5	9
Photophobia	5	9
Abdominal pain	3	6
Cough	2	4
Sore throat	1	2
<i>Signs</i>		
Splenomegaly	19	35
Hepatomegaly	16	30
Adenomegaly	9	17
Rhinitis	5	9
Primary lesion	4	7
Conjunctivitis	1	2
Edema	1	2

and non pruritic macules. A “tache noire” as described in Boutonneuse fever was not observed on any case, but a small pink macule approximately 3 mm in diameter was present on four children at the site of the tick bite.

Clinical symptoms, signs, and maximal variations in laboratory data observed in the patients are summarized in Tables 2 and 3.

Table 3. Laboratory findings in 54 children with Israeli spotted fever

Finding	Number	Percentage	Extreme of variation observed
SGOT >40 IU/ml	31/39	80	120 IU/ml
ESR >30 mm (first hour)	16/25	64	60 mm
Left shift (stabs >5%)	38/49	78	38%
Leucopenia (WBC <5000/mm ³)	17/53	32	3600/mm ³
Hyponatremia (Na <132 meq/l)	13/49	27	127 meq/l
Thrombocytopenia (<100000 platelets/mm ³)	3/50	6	46000/mm ³

No life threatening condition such as myocarditis or encephalitis was observed. Bleeding tendency was not seen in any of the 54 children. Thrombocytopenia, defined as a thrombocyte count below 100,000 platelets/mm³ was found in three (6%) of the 50 cases in whom this test was carried out (Table 3). In two of the three, the prothrombine time (PT), partial thromboplastin time (PTT), and fibrinogen split products determination (FSP) were within normal limits. In the third, although the PT was prolonged (17.5 sec vs. 11.5 sec in the control), disseminated intravascular coagulation was excluded by the finding of normal PTT, FSP, and thromboplastin time tests.

All cases responded to a three to seven day oral doxycycline regimen. Temperature returned to normal in less than three days following onset of therapy in 21 (39%) patients and between days three and five in the remainder. However, one patient became afebrile and antibiotics were discontinued after three days of therapy. He became febrile one day later. He was then treated with doxycycline for one week and recovered uneventfully.

Discussion

Spotted fever in Israel was first described as occurring in the Haifa bay area in 1946. At least one of these reported ten cases was fatal (Valero, 1949).

More recently, six hospitalized cases of spotted fever were reviewed in detail (Gutman et al., 1973). All were confirmed by rickettsial isolation or by immunofluorescent serological methods. All were adults with the exception of one 13-year-old male. One of these adult cases was considered as severe with encephalitis, acute renal failure, liver damage and myocarditis. Sixty-three cases of presumed spotted fever seen at Soroka medical Center from 1972 to 1978 inclusive have been reviewed. However, serological confirmation was lacking in an undetermined number of these (Schulchynska et al., 1982). Our series then represents the first review of children serologically confirmed to have had the disease. We cannot explain the preponderance of males, but a slightly higher

infection rate in males is also noted in Rocky Mountain spotted fever (Bradford and Hawkins, 1977).

The multisystemic involvement including the gastrointestinal, respiratory, and lymphatic system and integument is characteristic of the pathology due to a generalized vasculitis caused by the spotted fever group of rickettsiae (Walker and Mattern, 1980).

The clinical and laboratory findings in this study are similar to that described in Boutonneuse fever and in Rocky Mountain spotted fever in children (Linnemann and Janson, 1978; Moraga et al., 1982). However, the "tache noire" reported in one series to occur in $\frac{2}{3}$ of Boutonneuse fever patients (Moraga et al., 1982) and almost never occurring in Rocky Mountain spotted fever (Linnemann and Janson, 1978), was not observed by us. Hepatomegaly and splenomegaly may be more common in Israeli spotted fever than in Boutonneuse fever while the rate of lymphadenopathy may be lower.

All of the cases that we report were mild, i.e., recovery was in most uneventful after several days hospitalization and no serious life threatening sequelae developed. There are, however, reports of seven deaths due to laboratory confirmed spotted fever in Israel since 1973 (R. A. Goldwasser, personal communication).

A maculo-papular rash was one of the minimal diagnostic criteria for the inclusion of patients in our study. Thus, we do not describe those cases that may present without this sign. The frequency of cases lacking a rash and the frequency of subclinical infection is unknown. It has been noted, however, that up to 18% of a random sample of women at childbirth in Soroka Medical Center demonstrate antibodies to spotted fever group rickettsiae (Gross et al., 1983) compared to the reporting of about 50 cases annually among the regional population of approximately one quarter million. This leads to the speculation that many cases are not recognized, not reported, or that subclinical infection occurs. Spotted fever in Israel generally follows a seasonal pattern with most cases occurring in the warm months of the year. This seasonality is perhaps due to increased activity of man around tick habitats or increased numbers of ticks during the summer. In Israel, apparently identical rickettsiae have been isolated from *Rhipicephalus sanguineus* ticks removed from dogs and the blood of patients (Goldwasser et al., 1974). Sheep may also be infested with *Rhipicephalus sanguineus* ticks as well and be involved in the epidemiology of spotted fever (Gross and Hadani, 1984).

Spotted fever should be taken into account in the differential diagnosis of febrile disease in Israel and probably in neighboring countries as well.

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