Family Cluster of Rocky Mountain Spotted Fever

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Soon after a patient from Tennessee died of Rocky Mountain spotted fever (RMSF), several family members developed symptoms suggestive of the disease and were treated presumptively for RMSF. Fifty-four persons visiting the index patient's home were interviewed; serum samples were collected from 35. Three additional cases of RMSF were confirmed, all of which occurred in first-degree relatives. Time spent at the family home and going into the surrounding woods were significantly associated with developing antibodies to *Rickettsia rickettsii*. Ticks were collected and examined for rickettsiae by polymerase chain reaction analysis. Because hyperendemic foci and family clusters of RMSF can occur, when a case is suspected clinicians should be vigilant for signs and symptoms consistent with *R. rickettsii* infection in other persons who may have been similarly exposed.

Indeed, one of the characteristic features of the disease . . . is the rare occurrence of more than one case in a given family during a season. . . .

—Howard T. Ricketts, 1909 [1]

Rocky Mountain spotted fever (RMSF) is a tick-borne disease caused by *Rickettsia rickettsii*, the case-fatality ratio for which approaches 25% if untreated. Despite the availability of effective antibiotic therapy, the case-fatality ratio has remained at 4% to 10% since the 1950s [2–4]. The number of reported cases of RMSF in the United States has steadily increased over the past 5 years, and in 1996, cases were at their highest levels in over a decade [5]. Eighty-two percent of reported cases occurred in the South Atlantic and south central regions, with <2% of cases reported from the mountain states [5].

Although typically considered a sporadic disease, familial clusters of RMSF have been reported occasionally [6–11]. There have also been reports of foci ("islands") of disease hyperendemicity [12–21]. These foci have encompassed regions as large as entire counties [12, 13, 15] or areas of several square kilometers [12, 17, 18] and discrete geographical units including neighborhoods [22, 23] and urban parks [16]. The recognition of clustering of disease and islands of hyperendemicity is important for medical providers and public health personnel involved in treating and controlling the disease, because multiple infections can occur simultaneously or following identification of an index case.

Case Report

In August 1997, a previously well 49-year-old American Indian man from Tennessee presented to an emergency department in West Virginia, where he was traveling on business. He had a 5-day history of fever, headache, diffuse myalgias, and vomiting. The patient noted small red "chigger bites" around the ankles but recalled no recent tick bites. Physical examination revealed no identifiable source of infection, and no rash was noted. He was thought to have a viral illness and was discharged receiving symptomatic treatment. However, the symptoms increased, and 2 days later he was taken to a second hospital, where he presented with a temperature of 97.5°F, blood pressure of 112/84 mm Hg, respirations of 20/min, and pulse of 135/min. He appeared ill with clammy, mottled skin.

Laboratory studies disclosed a normal WBC count of 9.4×10^9/L, platelet count of 34×10^9 L, partial thromboplastin time of 42.7 seconds (normal range, 22–32 seconds), prothrombin time of 12.6 seconds (normal range, 11–14 seconds), and creatinine level of 415 μmol/L (4.7 mg dL). Within hours of admission, the patient became increasingly tachypneic, developed seizures and ventricular fibrillation, and died. Conjunctival hemorrhage and lower extremity petechiae were observed at death.

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An autopsy revealed pulmonary edema, mild splenic congestion, acute tubular necrosis of the kidneys, and hepatomegaly, but otherwise no specific cause of death was found. Approximately 1 month after his death, PCR testing and immunohistochemical staining of tissue specimens that were performed at the Centers for Disease Control and Prevention (CDC) revealed *R. rickettsii* in the endothelium of organs including brain, spleen, liver, kidneys, heart, and lung. The Tennessee State Health Department was notified, precipitating an investigation.

Although the patient lived in a primarily urban county, his home was on a heavily wooded lot in a semirural area. In the days preceding his funeral and before discovery of the cause of death, friends and relatives from eight states congregated at his home. Many of these individuals participated in a 72-hour American Indian ceremonial fire on the patient's property. The day after the funeral, the index patient's wife was admitted to the hospital and diagnosed with RMSF. Several other friends and family members subsequently developed symptoms compatible with the disease and were treated presumptively for RMSF.

Methods

A questionnaire was administered to persons reported to have spent time at the patient's home during the week between his death and the time of his funeral. Information was collected on demographic variables, symptoms, treatment, and medical history. Questions were asked about participation in the ceremonial fire, eating or smoking outdoors, going into the woods, tick exposure, repellent use, and other activities and behaviors potentially related to the risk of contracting RMSF.

Serum samples were obtained from consenting participants, and these specimens were tested for IgG antibodies to *R. rickettsii* by an indirect immunofluorescence assay (IFA) at the CDC [24]. Initial serum specimens were obtained 6–10 weeks after the index patient's funeral. Patients with positive antibody titers were asked for a second serum specimen 4–6 weeks later. Pathological specimens were tested for the presence of spotted-fever group (SFG) rickettsiae by using immunohistochemical staining [25] and PCR analysis. PCR products were sequenced and compared with known genetic sequences of rickettsiae [26].

A confirmed case of RMSF was defined as a clinically compatible illness (fever, headache, myalgia, or rash within 3 weeks of exposure) accompanied by a fourfold or greater change in the titer of antibody to *R. rickettsii* that was revealed by IFA testing of two separate serum specimens or by demonstration of SFG rickettsiae in a tissue specimen by immunohistochemical staining [27].

Ticks were collected from the index patient's home property and five similar control sites in the vicinity over a period of 2 successive days, 35 days after his funeral. The control sites included adjacent and nearby homes and properties within 3 miles that had similar vegetation, geography, pet ownership, and apparent use patterns. Flannel flags (1 m^2) were dragged over low vegetation in wooded and grassy areas and the edges of driveways, roads, paths, and dwellings and were examined for ticks approximately every 10 m. Ten CO_2 traps were also placed near the index patient's home at 10-m intervals along the perimeter of the yard for 6 hours. Ticks were identified and tested at the CDC for the presence of the rickettsial 17-kDa gene by PCR analysis according to a modification of previously reported techniques [28] (D. B. McKechnie, J. Hatfield, J. W. Sumner, C. D. Paddock, J. Olson, and R. F. Massung, unpublished data).

Statistical analyses were performed by χ^2 and Fisher's exact tests with use of Epi Info software [29].

Results

In addition to the index case, three confirmed cases of RMSF occurred after the funeral (table 1). Following the death of the index patient and before recognition of the cause of his death, his wife was the first person diagnosed with RMSF. The wife and brother of the index patient were both hospitalized because of severe febrile exanthematous illnesses within 2 weeks of the funeral. Both patients had a fourfold or greater rise in the titer of antibody to *R. rickettsii*. The index patient's sister developed a milder illness 2 weeks after the funeral and was treated successfully as an outpatient. A fourth seropositive individual, the son of the index patient, had evidence of antibody to *R. rickettsii* at a titer of 1:64, which persisted unchanged when retested 10 weeks later. He developed conjunctivitis and mild headache beginning 2 days after the funeral; his symptoms resolved without antibiotic therapy.

The investigation also identified another family member, a 13-month-old grandnephew of the index patient, who had died of RMSF 27 months before the index patient's funeral (table 1). The child had been living with the index patient's sister, ~5 miles from the index patient's home. He had spent time at the index patient's home before his death, although the family was unable to quantify this period and could recall no tick bites. Immunohistochemical staining of a tissue specimen that was obtained at autopsy of the child demonstrated SFG rickettsiae.

Fifty-five persons were identified as visitors or residents of the index patient's home during the week of his funeral. All but one (98%) of these persons—37 (67%) of whom lived in one of eight states outside of Tennessee—responded to the questionnaire. Thirty-five persons (65%) provided one or more serum specimens for testing; of these persons, 13 (37%) lived in Tennessee, and 22 (63%) lived in other states. After the wife's diagnosis, other family members were notified and urged to seek medical attention. Sixteen family members and friends of the index patient, all of whom spent time at his home during the week before his funeral, received doxycycline to either treat or avert RMSF. Fourteen of these persons were among those submitting serum specimens. Aside from the index patient's wife, brother, sister, and son who were mentioned above, none

Table 1. Clinical characteristics of five patients associated with a cluster of cases of RMSF confirmed by serological testing or immunohistochemical analysis.

Age (y)	sex	Relationship to index patient	Date of onset	Predominant signs or symptoms	Serum IFA titer: First sample	Second sample	Third sample	Antibiotic therapy	Outcome
49	M	Index	15 August 1997	Fever, headache, myalgias, vomiting	NA	NA	NA	None	Died; *Rickettsia rickettsii* identified at autopsy by immunohistochemical analysis and PCR testing
50	F	Wife	26 August 1997	Fever, headache, myalgias, rash	<1:40*	1:160*	1:1,024	Doxycycline	Well after 4-d hospitalization
56	M	Brother	8 September 1997	Headache, falling, rash, hyponatremia, thrombocytopenia	<1:64*	>1:512*	1:2,048	Doxycycline	Well after 12-d hospitalization
52	F	Sister	11 September 1997	Headache, myalgias, upper respiratory tract symptoms, cough	1:128	1:32	NA	Doxycycline	Resolved with outpatient treatment
1	M	Grandnephew	11 May 1995	Rash, fever, vomiting, diarrhea	<1:64*	NA	NA	Chloramphenicol	Died 27 mo before index patient's funeral; *R. rickettsii* identified at autopsy by immunohistochemical analysis

NOTE. IFA = indirect immunofluorescent antibody; NA = not available; RMSF = Rocky Mountain spotted fever.
* Serum samples tested at laboratories other than the CDC.

of these persons had titers of antibody to *R. rickettsii* at or above the cutoff titer of 1:64.

When funeral attendees with titers of antibody to *R. rickettsii* of ≥1:64 were compared with those with titers of <1:64, the presence of antibodies was associated with greater time spent at the family home during the week of the funeral, going into the woods surrounding the home, and being a first-degree relative of the index patient. Three of the five persons with evidence of recent or past infection with *R. rickettsii* resided at the index patient's home before his death. The ceremonial fire was attended by numerous persons for varying lengths of time, but the presence of antibodies to *R. rickettsii* was not correlated with length of time at the fire, collecting firewood, sitting on the ground, doing yard work, eating or smoking outside, not using insect repellents, noting a tick on one's body, or contact with the index patient's pet dog (who had not recently been ill).

Six hours of dragging flags yielded 133 ticks from the index patient's home property. In 12.5 hours of dragging flags at five control sites, only three ticks were collected. All ticks collected were identified as *Amblyomma americanum* (Lone Star tick) nymphs, except for one adult tick of the same species and a single *Haemaphysalis leporispalustris* (rabbit tick). PCR testing revealed the rickettsial 17-kDa gene in 10 of 11 pools of ticks (each pool contained ~13 ticks). Gene sequencing of the PCR products showed that the ticks harbored *Rickettsia amblyommii*, a newly recognized *Rickettsia* species [30] not known to be pathogenic for humans.

Discussion

These data document a cluster of RMSF that occurred in a single family and suggest that the focus of *R. rickettsii* had persisted in the same location or vicinity for at least 2 years. Although RMSF is generally sporadic, family clusters of disease have been recognized for >90 years [6–11, 20, 22, 31–63] (table 2). In some series, as many as 4% to 8% of all

Table 2. Previously reported family clusters of RMSF.

Year(s)	State(s)	No. of family members in cluster	No. of clusters reported	[Reference(s)]
1904–1987	AL, IA, IL, MD, MO, MS, MT, NC, NJ, NY, OH, RI, SC, TN, TX, VA, WV, WY, Mexico	2	51	[6–8, 10, 20, 22, 31–61]
1905–1973	IA, MS, MT, NC, WV, Mexico	3	9	[6, 9, 11, 32, 34, 43, 62]
1931	LA	4	1	[20]
1942	OK	6	1	[20, 63]

NOTE. RMSF = Rocky Mountain spotted fever.

Table 3. Reported geographic foci of RMSF in the United States.

Location	Period	No. of cases*	Nature of focus	[Reference(s)]
Wyoming	1895–1915	NS	Cases clustered in two central counties	[33]
Idaho	1914	386	Most cases clustered in six southern counties	[33]
Bitterroot Valley, Montana	1900–1980	400	Valley about 75 miles long	[32]
Cape Cod, Massachusetts	1955–1968	30	Cases concentrated in four areas on Cape Code and offshore islands	[12, 18]
Long Island, New York	1961–1988	59	Rate in East Hampton, Suffolk County, greater than that in other towns in area (overlaps with focus below)	[64]
Long Island, New York	1971–1976	124	80% of cases in New York during 1941–1970 occurred in Suffolk County; concentrated 2.2 km from shoreline	[21, 64]
Clermont County, Ohio	1962–1971	85	94-km^2 area in a suburbanizing county	[13]
Columbus, Ohio	1966–1981	28	28 cases in Franklin County occurred within 2 miles of this 0.11-km^2 (275-acre) area	[23]
Ohio	1981	S	Clermont, Franklin, and Lucas Counties (overlaps with two foci above)	[47, 65]
Virginia	1969	NS	Six counties in Piedmont plateau area with highest incidence	[66]
North Carolina	1970–1979	12	0.5-mile stretch of road in a small town in North Carolina. 12 cases in 40 households over 10 y	[22]
Alabama	1973	12	"Highly endemic spotted fever area in northwest Alabama"	[67]
Missouri	1974–1984	71	35% of cases in the state occurred in three counties	[68]
Mississippi	1975–1979	NS	Two-thirds of cases occurred in 14 contiguous counties in the north and northeast part of the state	[69]
North Carolina	1979–1981	NS	Cabarrus and Rowan Counties; rate of RMSF four times that in North Carolina and 30 times that in the U.S.	[15, 70]
Texas	1979–1988	NS	Nine counties in north central Texas reporting >10 cases	[71]
Tarrant County, Texas	1983	8	6.4 × 9.6-km area where eight cases occurred in 2 mo	[17]
Oklahoma	1981–1985	NS	Cases concentrated in 10 central counties	[72]
South Carolina	1985–1990	NS	Four counties with increased incidence	[73]
New York City	198–	4	Near Soundview Park, Bronx	[16]
Delaware	1996	4	Children at summer camp	[74]

NOTE. NS = not specified; RMSF = Rocky Mountain spotted fever.

patients with RMSF were part of family clusters [2, 22]. Similarly, the concepts of islands or foci of disease hyperendemicity have been noted previously (table 3) [12–23, 32, 33, 47, 64–74]. Such foci have included areas of several square kilometers with persistently high rates of disease over periods of several years and rarely family members acquiring disease simultaneously. Our cluster apparently occurred from exposure around a single home.

The reasons for focal clustering of RMSF could include variable distribution of tick populations, focal areas of increased tick infection with *R. rickettsii*, increased rickettsial virulence or host susceptibility, new incursions of humans into tick-infested areas, or a combination of these factors. The potential of dogs as a possible reservoir of *R. rickettsii* is debated [75], and in this study, direct contact with the family dog was not correlated with disease. *R. rickettsii* is passed transovarially from adult females to their progeny; therefore, foci may be expected to occur. Several studies have estimated that ≤1% of ticks may carry pathogenic *R. rickettsii* even in areas of endemicity [65, 76]. Although some studies have not found differences in distribution of infected ticks related to rates of disease [12, 13, 77–79], other investigators have noted a correlation [16, 21, 65].

In the eastern United States, the primary vector of *R. rickettsii* is *Dermacentor variabilis* (American dog or wood tick) [4]. Whether the Lone Star tick *A. americanum* also transmits the disease is debated [3, 4, 67]. Many of the people interviewed in this study described large numbers of small, pinpoint-sized brown "seed ticks" at the home and on their bodies, and other persons denied tick bites but noted numerous itchy red "chigger bites" around the ankles. Seed ticks are the small, six-legged larval stage of hard ticks, including *A. americanum*, and these ticks can be difficult to see and identify. Some reports suggest that larval *A. americanum* ticks are capable of biting humans and transmitting *R. rickettsii* [80], which may account for some cases of RMSF without a recognized history of tick bite [81].

Only *A. americanum* ticks were collected from the index patient's property in this study, although collection did not occur until 5 weeks after his death. Possibly, the tick population had changed in the 5-week interval between his death and collection, and *D. variabilis* was the vector in this cluster but was not present at the time of collection. The patient's property was heavily wooded, with habitat that would support populations of both species. No obvious factors were apparent to account for the clustering of ticks at the index site, compared

with the remarkably lower rate of tick collection from adjacent properties.

This investigation used PCR analysis and gene sequencing to identify rickettsiae: *R. amblyommii* was found, but there was no evidence of *R. rickettsii*. The PCR technique amplified and allowed specific identification of DNA from the predominant rickettsial species in the tick pools. The sensitivity of the technique is not known. Possibly, lower levels of *R. rickettsii* were present in this tick population but went undetected by this method.

Only seven of the 16 persons in this investigation who were treated empirically for RMSF had any type of rash. Previous studies of RMSF suggest that the characteristic rash may be absent in 5% to 34% of patients [2–4, 64, 82] and that only one-half may have a rash within the first 3 days [82]. Lack of a rapid diagnostic test for RMSF necessitates treatment based on the history and results of physical examination plus a high index of suspicion. Only three (21%) of the 14 symptomatic persons treated presumptively from whom serum samples were available had antibodies to *R. rickettsii* at titers of >1:64. It has been reported that treatment with antibiotics within the first few days of disease onset may blunt the development of antibodies detectable by CF and microagglutination testing [83–86] but that other tests are less affected [85]. This phenomenon has not been extensively studied with the IFA test.

One person who provided serum samples but was not treated for RMSF had a titer of IgG antibody to *R. rickettsii* of 1:64, which was unchanged when tested again 10 weeks later. He often worked in the woods near the family home and had a long history of frequent tick bites; however, he had never been diagnosed with RMSF and could not recall a specific illness suggestive of the disease. This case may represent a stable, persistent antibody titer from a previous asymptomatic or unrecognized infection with *R. rickettsii* or possibly another SFG *Rickettsia*. Serosurveys have revealed detectable titers of antibody to SFG rickettsiae in 11% to 21% of sixth graders [17, 87] and 29% of adults in areas of endemicity [70]. The existence of asymptomatic infections is debated [4], although the lack of specificity of symptoms makes unrecognized mild infections likely.

This cluster is a salient example of the importance of considering RMSF in the differential diagnosis of patients with febrile illnesses who present in the spring and summer in areas of endemicity. Prophylactic treatment of asymptomatic persons exposed to ticks is not recommended [88, 89], even in areas where RMSF is endemic. However, because of a lack of specific symptoms or a rapid diagnostic test, empirical treatment of persons with suspected cases is often necessary. Although Ricketts [1] long ago noted their "rare occurrence," family clusters and hyperendemic foci of RMSF may be more common than appreciated. When a case of RMSF is suspected, it is important for family members and physicians to remain vigilant for signs or symptoms consistent with *R. rickettsii* infection in other persons who may have been similarly exposed.

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