Clinical significance of *Rickettsia rickettsii* antibody testing among children in Eastern Long Island, New York

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Background

- Rocky Mountain spotted fever (RMSF) is a tickborne illness caused by *Rickettsia rickettsii.*
- Infection carries a high risk of morbidity and mortality, particularly when there is a delay in starting appropriate antibiotics.
- Clinical features of RMSF are non-specific. The classic triad of fever, rash, and headache is a helpful but poorly sensitive tool for case identification.
- Serology is the gold standard diagnostic tool, yet has low sensitivity early in infection. Our experience and prior publications suggest specificity may be also be low, particularly among patients without symptoms suggestive of RMSF. [1, 2]
- Doxycycline is sometimes prescribed without clear exposure history or RMSF symptoms.

Study Aims

- To describe serology results, particularly the false-positive antibody rate, in a region with low RMSF incidence.
- To describe the symptomatology of children undergoing RMSF testing.
- To describe antibiotic prescriptions among children tested for RMSF.

Methods

- Retrospective chart review of patients ≤ 21 years old with ICD codes for RMSF and/or underwent testing for *Rickettsia rickettsii* antibodies in the Stony Brook University Hospital (SBUH) system between 2010-2020.
- Charts without clinical notes were excluded.
- Data collected includes patient demographics, presenting symptoms, laboratory results, treatments, and clinical outcomes.
- Patients were classified as 'confirmed', 'probable', 'suspected' as per the CDC definitions. 'Negative' and 'unlikely' are SBUH-defined classifications. (Table 1)
- Descriptive statistics were calculated.
- False-positive antibody defined as those with 'unlikely' RMSF.
- True-positive antibody defined as those with 'confirmed' or 'probable' RMSF.

Table 1: Clinical and laboratory definitions used to classify study participants [3]

Clinical criteria:	**Fever and ≥1 other symptom**: rash, eschar, headache, myalgia, anemia, thrombocytopenia, or hepatic transaminase elevation		
Laboratory criteria:	**Confirmatory laboratory evidence**	Fourfold increase in *R.r.* IgG between acute and convalescent testing	
	Presumptive laboratory evidence	Elevated IgG titer **≥1:128** reactive within 60 days of illness onset	
	Supportive laboratory evidence	Elevated IgG titer **<1:128** reactive within 60 days of illness onset	
RMSF case classifications:		**Clinical classification:**	**Laboratory classification:**
	Confirmed	Meets criteria	Confirmed
	Probable	Meets criteria	Presumptive
	Suspected	Meets criteria	Supportive
	Unlikely	Does not meet criteria	Single positive *R.r.* IgM and/or IgG
	Negative	Does not meet criteria	Negative *R.r.* IgM and IgG

Results

- 172 patients met inclusion criteria.
- Mean age: 14.7 years old (range: 11 months to 21 years old). 56% were male
- 23% reported a recent witnessed tick bite.
- Patients were categorized into all 5 case classifications. (Table 2)

Table 2: Number of patients in each classification with rate of symptoms, abnormal lab values, and doxycycline treatment

	Confirmed	Probable	Suspected	Unlikely	Negative
n (%)	2 (1.2%)	3 (1.7%)	10 (5.8%)	14 (8.1%)	143 (83.1%)
Fever	2	3	10	1	72
Rash	2	2	7	3	55
Headache	2	2	6	4	54
Myalgia	1	0	3	1	27
Anemia	2	1	5	1	32
Thrombocytopenia	2	1	4	0	20
Elevated LFT	2	1	6	2	37
Patients treated with doxycycline	2 (100%)	2 (66.7%)	8 (80%)	5 (35.7%)	28 (19.6%)

Serology:

- True-positive RMSF antibodies occurred in 2.9% (n=5).
- False-positive RMSF antibodies occurred in 8.9% (n=14).

Symptoms:

- Of RMSF classic triad symptoms, 52% of participants had fever, 41% rash, and 44% headache. (Table 2)
- All 3 triad symptoms occurred in 2/2 (100%) proven cases, but only 1/3 of 'probable' or 'suspected' cases.
- Combination of anemia, thrombocytopenia, and transaminitis occurred in 2/2 (100%) proven cases, but only 1/3 of 'probable' and 0/10 of 'suspected' cases.

Antibiotics:

- 36% of patients with false-positive and 20% with negative serology received doxycycline.
- Of the 33 'unlikely' and 'negative' patients that received doxycycline, 5 had a final diagnosis of Lyme/tick bite/tick borne illness, 1 had sepsis, 1 had pneumonia, 1 had strep throat, 1 had Dengue fever and 1 had encephalitis.

Conclusion

- Among children in a low-incidence region, RMSF antibodies were frequently obtained without signs of infection, including half without fever.
- 1.1% met CDC criteria for confirmed RMSF, consistent with the rarity of the disease in our region.
- False-positive rate was 3 times higher than the true-positive rate and nearly 10% of all tests performed.
- Clinical triad of fever, rash and headache was identified in 100% of those with confirmed RMSF but not among those with other RMSF case classifications.
- Anemia, thrombocytopenia and transaminitis was also identified in 100% of those with confirmed RMSF.
- Careful consideration of symptoms and routine laboratory testing results should be considered prior to initiating doxycycline treatment for presumptive RMSF. Many patients in our cohort did not have suggestive findings.
- 26% of patients received doxycycline despite only 1.1% meeting criteria for confirmed RMSF.
- The cause of false-positive IgG is unclear, but may be due to cross-reactivity to *Rickettsia amblyommatis* and Lyme disease [4]. Alternatively, it is possible a more mild form of RMSF exists than has been traditionally described, signifying true-positive antibodies among those without a severe illness.

Limitations

- Single center study using a relatively small sample size.
- Retrospective study designs prevent systematic evaluation of infection signs, symptoms, and exposures.
- True RMSF cases may have been missed due to the frequent lack of convalescent titers.

References

1. Buckingham, S.C., *Tick-borne diseases of the USA: Ten things clinicians should know.* J Infect, 2015. **71 Suppl 1**: p. S88-96.

2. McQuiston, J.H., et al., *Inadequacy of IgM antibody tests for diagnosis of Rocky Mountain Spotted Fever.* Am J Trop Med Hyg, 2014. **91**(4): p. 767-70.

3. Centers for Disease Control and Prevention. (2021, April 16). *Rocky Mountain spotted fever (RMSF) (Rickettsia rickettsii) 2008 case definition*. Centers for Disease Control and Prevention. Retrieved September 29, 2022, from https://ndc.services.cdc.gov/case-definitions/rocky-mountain-spotted-fever-2008/

4. Apperson CS, Engber B, Nicholson WL, Mead DG, Engel J, Yabsley MJ, Dail K, Johnson J, Watson DW. Tick-borne diseases in North Carolina: is "Rickettsia amblyommii" a possible cause of rickettsiosis reported as Rocky Mountain spotted fever? Vector Borne Zoonotic Dis. 2008 Oct;8(5):597-606. doi: 10.1089/vbz.2007.0271. PMID: 18447622.