Am. J. Trop. Med. Hyg., 81(2), 2009, pp. 187–188

Editorial

Sennetsu Neorickettsiosis: A Potentially Prevalent, Treatable, Acutely Incapacitating Tropical Infectious Disease

David H. Walker*

Department of Pathology, WHO Collaborating Center for Tropical Diseases, University of Texas Medical Branch at Galveston, Galveston, Texas

Newton and others have detected a potentially prevalent acute febrile disease very likely associated with consumption of raw fish in tropical Asia.[1] The etiology of sennetsu neorickettsiosis, a truly neglected infectious disease, was determined in Japan more than 50 years ago.[2] In this issue of *American Journal of Tropical Medicine and Hygiene*, a team from Vientiane, Oxford, Kuala Lumpur, Bangkok, and Marseille reports four important findings: 1) the definitive diagnosis of sennetsu neorickettsiosis in Laos; 2) the first detection of *Neorickettsia sennetsu* in a fish, its likely vector to humans; 3) seroprevalence in populations of febrile patients (14–15%) and healthy persons (17%) in Laos and of febrile patients (3%) in Thailand, suggesting a high undiagnosed incidence of sennetsu neorickettsiosis in southeastern Asia; and 4) the discovery of novel *Neorickettsia* in fish.

The work emphasizes the power of molecular methods, which exerted tremendous impact on our concept of the importance of this infectious disease by the identification of *N. sennetsu* in a single patient and a single fish. The observed seroprevalence data may actually underestimate the incidence of sennetsu neorickettsiosis as suggested by the absence of antibodies in the infected patient 44 months after his acute illness. If antibodies do not persist for long after infection, the actual burden of disease might be even greater than suggested.

Neorickettsia are obligately intracellular bacteria of the order Rickettsiales, family Anaplasmataceae, which also includes tick-borne *Anaplasma*, *Ehrlichia*, and *Wolbachia* symbiotes of arthropods and filaria. The working model of the zoonotic cycle of *N. sennetsu* is that the bacteria infect trematodes that parasitize fish. Vertebrates that eat uncooked fish containing infected flukes may be either definitive or incidental hosts.

The research team in Laos wisely conserved a prospective bank of sera from patients with acute febrile illness. Many such neglected diseases are hidden under the umbrellas of major infectious diseases such as malaria, arboviral infections, and typhoid fever for which a confirmatory diagnosis may not be established in many clinically diagnosed patients.[3–6] This situation leads to failure to detect some diseases such as sennetsu neorickettsiosis, rickettsioses, and ehrlichioses for which there is effective treatment that differs from that of malaria or of viral infections, for most of which there is currently no effective treatment. It is disappointing that so many scientific studies are focused on a single agent or group of agents and do not address the etiology of the illnesses that are not determined to be that of the investigators' particular interest. International and philanthropic institutions have placed emphasis on diseases considered to have the greatest disability-adjusted days of life lost (DALYs). Diseases that are not studied and are technologically difficult to study, of course, would be assigned low DALYs; thus, reducing the likelihood that they would receive the attention that would determine their actual significance and address their control.

As characteristically described, patients with sennetsu neorickettsiosis experience sudden onset of chills and fever, which rises to 38–39°C and lasts for approximately 2 weeks. Other common manifestations are headache, malaise, myalgias, arthromyalgia, pharyngitis, and generalized lymphadenopathy.[7] The number of patients who have these symptoms and signs and are not evaluated for the diagnosis of neorickettsiosis is enormous, essentially all of them. The fact is that if treated with a tetracycline antimicrobial such as doxycycline patients with neorickettsiosis defervesce in 1–2 days with prompt subsidence of the other symptoms.

Gaps in our knowledge of sennetsu neorickettsiosis include its incidence, geographic distribution, and risk factors. Although the research tools used by Newton and others were effective in establishing evidence of the presence of *N. sennetsu* and of antibodies to the agent in their study, routine diagnostic methods for use under conditions of limited resources need to be developed and validated. For example, although an arbitrary immunofluorescent antibody assay titer of ≥ 100 and Western immunoblot detection of an approximately 57 kDa antigen are reasonable for a research study, these methods are challenging to apply in the field. It would be useful to determine the relationship of the identified Western immunoblot band to the major 51 kDa antigenic protein of *Neorickettsia risticii* that is also present in *N. sennetsu*.[8] Other significant gaps in knowledge include elucidating the zoonotic cycle of *N. sennetsu*, its trematode host and anatomic location in fish, and mechanisms of pathogenesis and immunity including susceptibility to reinfection. It is likely that these gaps remain wide open opportunities for study.

Neorickettsia are not confined to Asia. Indeed, two species have been identified in North America. *Neorickettsia helminthoeca* causes salmon poisoning disease that is recognized mainly in dogs,[9] and *N. risticii* is a very close relative of *N. sennetsu*. Although the apparent risk of *N. risticii* infections of humans in North America would be minimal as the ordinary diet does not include uncooked snails, insects, or bats,[10] the true number of *Neorickettsia* species and their ecologic cycles in North America and Europe has hardly been explored. Ultimately, understanding neorickettsial ecology requires knowledge of the *Neorickettsia*-trematode interactions. The three known trematode hosts of *Neorickettsia* belong to three different suborders, *Plagiorchiata (N. risticii), Opisthorchiata* (*Stellantchasmus falcatus* agent), and *Troglotremata (N. helminthoeca)*, suggesting that the universe of *Neorickettsia* may be much larger than currently appreciated.

*Address correspondence to David H. Walker, Department of Pathology, WHO Collaborating Center for Tropical Diseases, University of Texas Medical Branch at Galveston, 301 University Blvd., Keiller Bldg., Galveston, TX 77555-0609. E-mail: dwalker@utmb.edu

Author's address: David H. Walker, Department of Pathology, WHO Collaborating Center for Tropical Diseases, University of Texas Medical Branch at Galveston, 301 University Blvd., Keiller Bldg., Galveston, TX 77555-0609, Tel: 409-772-3989, Fax: 409-772-2500, E-mail: dwalker@utmb.edu.

REFERENCES

1. Newton P, Rolain JM, Rasachack B, Mayxay M, Vathanatham K, Seng P, Phetsouvanh R, Thammavong T, Zahidi J, Suputtamongkol Y, Syhavong B, Raoult D, 2009. Sennetsu neorickettsiosis: a probable fish-borne cause of fever rediscovered in Laos. *Am J Trop Med Hyg 81:* 190–194.
2. Misao T, Kobayashi Y, 1953. Studies on infectious mononucleosis. I. Isolation of etiologic agent from blood, bone marrow, and lymph node of a patient with infectious mononucleosis by using mice. *Tokyo Iji Shinshi 71:* 683–686.
3. Ndip LM, Bouyer DH, Travossos Da Rosa APA, Titanji V, Tesh RB, Walker DH, 2004. Acute spotted fever rickettsiosis among febrile patients, Cameroon. *Emerg Infect Dis 10:* 432–436.
4. Ndip L, Fokam E, Bouyer DH, Ndip R, Titanji PK, Walker DH, McBride J, 2004. Detection of *Rickettsia africae* in patients and ticks along the coastal region of Cameroon. *Am J Trop Med Hyg 71:* 363–366.
5. Medina-Sanchez A, Bouyer DH, Alcantara-Rodriguez A, Mafra C, Zavala-Castro J, Whitworth T, Popov VL, Fernandez-Salas I, Walker DH, 2005. Detection of a typhus group *Rickettsia* in *Amblyomma* ticks in the state of Nuevo Leon, Mexico. *Ann NY Acad Sci 1063:* 327–332.
6. Zavala-Velazquez JE, Yu X-J, Walker DH, 1996. Unrecognized spotted fever group rickettsiosis masquerading as dengue fever in Mexico. *Am J Trop Med Hyg 55:* 157–159.
7. Tachibana N, 1986. Sennetsu fever: the disease, diagnosis, and treatment. Leive L, ed. *Microbiology-1986.* Washington, DC: American Society for Microbiology, 205–208.
8. Rikihisa Y, Zhang C, Kanter M, Cheng Z, Ohashi N, Fukuda T, 2004. Analysis of *p51, groESL*, and the major antigen P51 in various species of *Neorickettsia*, an obligatory intracellular bacterium that infects trematodes and mammals. *J Clin Microbiol 42:* 3823–3826.
9. Rikihisa Y, Stills H, Zimmerman G, 1991. Isolation and continuous culture of *Neorickettsia helminthoeca* in a macrophage cell line. *J Clin Microbiol 29:* 1928–1933.
10. Gibson KE, Rikihisa Y, 2008. Molecular link of different stages of the trematode host of *Neorickettsia risticii* to *Acanthatrium oregonense. Environ Microbiol 10:* 2064–2073.