Newton and others have detected a potentially prevalent acute febrile disease very likely associated with consumption of raw fish in tropical Asia. The etiology of sennetsu neorickettsiosis, a truly neglected infectious disease, was determined in Japan more than 50 years ago. 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 flakes 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 infectious diseases such as malaria, arboviral infections, and 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

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. 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. 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, 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, 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.
REFERENCES


