More Q's than A's in Chronic Q Fever Hepatitis

Jihad Bishara MD

Infectious Disease Unit, Rabin Medical Center (Beilinson Campus), Petah Tiqva, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Seventy years ago an outbreak of an "enigmatic" febrile illness occurred in a meat factory in Brisbane, Queensland, Australia. In 1937, Derrick [1] coined the term "Q" for "query" since no etiologic agent was identifiable. Subsequently, the organism was isolated from the blood and urine of these patients and was identified by Burnet and Freeman [2] as a rickettsia. In 1938, Davis and Cox [3] isolated the same organism, which was found in ticks, and this organism was subsequently referred to as *Coxiella burnetii*.

C. *burnetii* is a small, obligate intracellular Gram-negative bacterium. Phylogenically, the organism falls within the gamma group of proteobacteria close to other intracellular pathogens, such as Legionella sp., *Francisella tularensis*, and Rickettsiella sp. [4]. The most common reservoirs of this bacterium are domesticated ruminants, primarily cattle, sheep and goats. Humans typically acquire Q fever by inhaling aerosols or contaminated dust derived from infected animals or animal products [5].

C. *burnetii* is a highly infectious agent; it is resistant to heat, drying, environmental factors, and chemical agents including common disinfectants, and has the ability to survive for long periods in the environment [4]. It can become airborne and inhaled by humans. A single C. *burnetii* organism may cause disease in a susceptible person. This agent could be developed for use in biological warfare [6].

Q fever is a protean disease, manifesting in acute and chronic forms. Raoult et al. [7] reported the clinical and epidemiologic features of 1,383 cases of Q fever over a 14 year period; 77% were considered acute and 23% chronic. The most common reported diseases manifesting in the acute form of Q fever are hepatitis, pneumonia, pneumonia with hepatitis, isolated fever and, rarely, meningitis, meningoencephalitis, perimyocarditis [7] and acalculous cholecystitis [8]. The most common form of chronic Q fever in Raoult's study was endocarditis (73%), with chronic hepatitis accounting for 3% of the cases. Less frequent manifestations of chronic Q fever included osteoarticular infection, chronic pericarditis, adenopathies, neuropathy, and splenic and lung pseudotumor [7].

In this issue of *IMAJ,* Galperin and co-workers [9] report a case of chronic Q fever hepatitis in a 69 year old woman who presented with fever of 2 weeks duration, weakness, frontal headache, and elevated liver enzymes. On admission, indirect immunofluorescence antibody assay showed immunoglobulin G antibodies reactive with *C. burnetii* phase II antigen of titer 1:6,400, compatible with acute Q fever infection. Subsequent IFA assays showed the predominance of IgG antibodies to C. *burnetii* phase I antigen, demonstrating the transformation of acute to chronic Q fever. The authors conclude that the patient had acute Q fever hepatitis that had progressed to chronic Q fever hepatitis. She was treated with doxycycline and ciprofloxacin. At 3 months follow-up, the patient was asymptomatic with slightly elevated liver enzymes [9].

As noted by the authors, the literature pertaining to antibiotic therapy of chronic Q fever hepatitis is scarce. The combination of doxycycline and hydroxychloroquine for a mean of 18 months was shown to be the optimal regimen for Q fever endocarditis [10]. Unfortunately, a liver biopsy was not performed in this case. Because of the rarity of such cases, pathologic examination, culture and polymerase chain reaction assay for *C. burnetii* from liver tissue are crucial and might clarify this rare and enigmatic entity.

The variation in clinical expression of Q fever may be organism-related, based on different plasmid types or variations in organotropism by six strains of *C. burnetii* that are diverse in various geographic areas. This could explain, in part, the predominance of pneumonia in North America versus the high proportion of hepatitis in France and Europe [11]. Raoult and associates [7] favor host factors to explain these differences. Hepatitis was found to be more prevalent in younger patients and pneumonia more common in the elderly and those who are immunocompromised. Isolated fever was most common in women. There is no evidence that isolates from chronic and acute human infections differ when collections are tested either by PCR or lipopolysaccharide-specific monoclonal antibodies [4]. The major predisposing condition for the chronic form of the disease is valvular disease with endocarditis [7].

Experimental data on host factors reveal the protective role of 17ß estradiol in mice, which explains why Q fever in pregnant animals becomes chronic. *C. burnetii* remains in the uterus and mammary glands and can be reactivated in subsequent pregnancies [4]. Whether this is the reason for the development of chronic Q fever hepatitis in the described postmenopausal woman needs to be explored further. During chronic Q fever, the immune response is ineffective. *C. burnetii* continues to multiply

IFA = immunofluorescence antibody
IgG = immunoglobulin G
PCR = polymerase chain reaction

despite high concentrations of IgG, M and A to phase I and II antigens. Monocytes do not migrate through the endothelium and high levels of interleukin 10 are secreted. When this key factor is inhibited by antibodies, microbicidal properties of macrophages from patients with chronic Q fever are restored, as is their ability to migrate across the endothelium [4].

Despite the substantial progress made during the last seven decades, there are still many unanswered questions regarding this remarkable "query" disease. Further investigation into chronic hepatitis is needed to determine which patients are at risk to develop chronic Q fever hepatitis. What is the natural history of the disease? How can the progression of acute Q fever hepatitis to the chronic form be prevented? What is the real incidence of this form of Q fever disease in Israel and worldwide? What is the optimal combination and duration of antibiotics for the treatment of chronic Q fever hepatitis?

The report by Galperin and team enhances our knowledge about a rare form of a not uncommon but infrequently recognized disease. Chronic Q fever hepatitis should be included in the differential diagnosis of any form of acute or chronic liver disease of unknown etiology.

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Correspondence: Dr. J. Bishara, Infectious Disease Unit, Rabin Medical Center (Beilinson Campus), Petah Tiqva 49100, Israel.
Phone: (972-3) 937-6310
Fax: (972-3) 922-1605
email: bishara@netvision.net.il

Capsule

Stem cells therapy ASAP

Escolar and collaborators provide an example of how very early stem cell therapy can enhance the chance of success. The study group consisted of newborns suffering from Krabbe's disease, a rare genetic disorder in which loss of a lysosomal enzyme in cells resident in the central nervous system allows the lipid substrates to accumulate, which results in severe neurologic deterioration and death. In an attempt to correct this deficiency, stem cells from banked umbilical cord blood of unrelated donors were transplanted into newborns who either had already started to develop symptoms (142 to 352 days old) or had a family history of the disease but were as yet asymptomatic (12 to 44 days old). In the latter group, survival and neurologic development were significantly improved for almost all graft recipients, with cognitive functions in the normal range. Presymptomatic therapy in this case is likely to have allowed more efficient stem cell replacement of defective resident cells, thus avoiding some of the early toxic effects of the lipid substrates on young neurons and immature neural tracts.

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Eitan Israeli

Capsule

Making muscle from test tube to mouse

Bone marrow stromal cells are generally known as being the source of skeletal tissue. Dezawa and co-workers have shown how to efficiently direct the bone marrow stromal cells of human and rat toward muscle cell fate. The defined cell culture conditions include modifying the cells to express a portion of the signaling molecule Notch. The treated cells fuse to form myotubes in culture and can be incorporated into the muscles of dystrophic mice and into the degenerated muscles of rats.

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Eitan Israeli