Two Detailed Case Histories Involving Patients with Co-Infections

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Brief Abstract

Medical and laboratory data from a patient marital couple illustrate the potential seriousness and persistence of increasingly common protozoan, rickettsial, and spirochetal infections. Such case histories demonstrate immediate need for intensive education of all physicians and the public about the risks posed by tick-borne infections. Experiences of these 2 patients demonstrate necessity for accurate epidemiological reporting of all such vector-borne diseases. Of the titled infections, only Lyme and ehrlichiosis are on the Center of Diseases Control's list of Officially Reportable Diseases.

Descriptions of the patients' symptoms

Mr. W's infection— unrecognized chronic Lyme disease initiated a medical controversy

Mr. W, an active 76-year-old man (1996) upon his first ever visit to a psychiatrist's office, needed evaluation due to marked changes in his personality. Careful history-taking revealed that he had experienced a rectangular dark red rash on 1 ankle (otherwise asymptomatic) for several weeks circa June 1996. By late that summer, he had gradually developed uncharacteristic and inappropriate outbursts of extreme irritability, altered gait, loss of direction sense, evening chills, episodic daytime sleep urgency, pronounced executive memory loss and variable loss of recent memory. Neurologic and psychiatric workups ensued. In September 1996, his neurologist diagnosed Lyme disease (LYD) when an enzyme-linked immunosorbent assay blood test revealed a positive IgG of 2.63. Doxycycline 100 mg twice daily was begun. Mr. W became less symptomatic, his rages abated, and his memory improved. Another specialist, however, questioned accuracy of the diagnosis, terminating the antibiotic after 2 weeks. Axillary lymphadenopathy remained unexplained.

As June 1997 approached, Mr. W's sore left knee was visibly swollen. Nine months after original diagnosis, he also had developed balance problems, strange, shifting, tender, acutely painful areas on his scalp and feet, and a highly distracting, tingling sensation on the tip of his nose. His family physician examined him and confirmed the original diagnosis of persistent, neuro-Lyme disease.

On 6/3/97, prior to antibiotic treatment, Mr. W suddenly experienced an episode of violent, seizure-like shaking of his entire body, during which he did not lose consciousness. (1,2) There were no urinary tract or other symptoms. His LYD Western Blot (WB) test (7/9/97) revealed 4 highly significant positive IgG bands plus another: an equivocal band on the same WB test for immune antibodies relating to the causative spirochete, *Borrelia burgdorferi* (Bb).(3)

Gradually improving but still symptomatic following several months of oral antibiotics, Mr. W's WB immune response increased to show 6 positive, significant, IgG antibody bands against Bb. (4/8/98). Intensive antibiotic treatment consisted of concomitant oral cefuroxime axetil, cefixime and doxycycline 100 mg three times per day. His knee swelling totally subsided. Later, receiving azithromycin alone, the patient's irritability, disorientation, cognitive problems, and all but 2 other symptoms resolved. He retained his intense need for lengthy daytime naps despite sound nighttime sleep and he experienced episodic afternoon chills despite normal body temperature. He had episodes of dark urine. Diagnostically, however, physicians did not consider babesiosis early on.

When waves of daytime narcoleptic-like sleep attacks and chilliness intensified during evening hours, despite the use of antibiotics, and Mr. W complained that winter's coldness depressed him, he was further evaluated. On 3/26/98, his blood tested positive with a 1:512 indirect fluorescent antibody (IFA) titer for *Babesia microti* at BBI (now "Specialty") Laboratory. His *B microti* polymerase chain reaction (PCR) was also positive (7/7/98) at Medical Diagnostic Laboratories (MDL). Treatment rounds of anti-protozoan medications atovaquone (Mepron) and azithromycin (Zithromax) were undertaken for babesiosis.

Overview of the husband's follow-up laboratory findings and treatment of babesiosis

Fifteen months into treatment by a LYD specialist (4) for chronic babesiosis and LYD, the patient's *B microti* PCR turned negative but his *B burgdorferi* DNA (PCR at MDL) was positive. Mepron was stopped and antibiotic treatment continued. When symptoms resurged in approximately 1 year concomitant with an increasing Human Monocytic Ehrlichiosis (HME) titer, restarting his doxycycline (9/27/00) provided general relief and resolution of lymphadenopathy. However, by April 2001, Mr. W's disorientation, chilliness and sleep urgency intensified once more. His PCR for *B microti* DNA again returned positive, as did his WB for the same organism (MDL).

Because of the positive direct blood test for *B microti* DNA, clinical improvement from LYD symptoms, and the first time fully negative Lyme IgG WB, new emphasis began on re-treatment of chronic babesiosis (5/02). Mr. W received the anti-malarial, Malarone (atovaquone with proquanil), but he also was given a course of dirithromycin (Dynabac) to maintain suppression of likely persistent subclinical borrelial infection. Rationale was that presence of co-infections greatly magnified severity of each. Eventual return of original Lyme disorientation and knee symptoms, however, unveiled resurgences of Lyme WB IgG antibodies (now up to 7 significant bands, 1/30/02—IGeneX Lab) and at MDL, an increase to 3 Babesia antibody bands.(5) At no time did Mr. W need psychotropic medications, other than the stimulant described below.

Interpretation of Mr. W's experience with babesiosis

Mr.W had multiple cycles of treatment with antimicrobial medications (atovaquone, azithromycin, and a combination of atovaquone and proquanil) throughout 4 years with much improvement in memory, affect and general health. Both direct PCR evidence of *Babesia* infection and indirect Babesia tests (increasingly positive antibodies) remained confirmatory of his having active chronic babesiosis. When anti-babesia medication lapsed, there were returns to lab and clinical abnormalities.

Persistent daytime sleep urgency despite lengthy antimicrobial treatment, and 6 PM daily chills, may have been residual signs of chronic babesiosis. However, the narcolepsy-like symptom cannot totally be separated from LYD. Direct evidence of both Lyme and babesiosis was still present by positive DNA testing in April 2001 and by increasing antibodies to both in January 2002. Recent intensification of his sleep attacks coincident with current absence of anti-protozoan treatments suggests babesiosis causation. Modafinil (Provigil) 200 mg twice daily greatly improved his wakefulness. Recent developments of positive PCRs for mycoplasma, HHV-6 and a newly developed mild sleep apnea imply possibility of additional causations of his increasing sleep urgency. Of significance, likewise, there are now diminished blood levels of androstenedione, ACTH, ADH and MSH and increased osmolality—a syndrome frequently seen following illness due to chronic neurotoxic diseases (6) such as Lyme disease and a methicillin-resistant coagulase-negative naso-pharyngeal infection that was diagnosed and treated.

Mrs. W's infections, laboratory findings and treatment

Mrs. W's initially unrecognized tick-borne disease manifested neurologically and muscularly. A 66-year-old gardener, she accompanied her husband for evaluation. She described a medically-observed, ring-shaped red rash on the skin of one forearm (1990). At least 3 other similar rashes were observed in the years surrounding that event—2 had the appearance of a "bull's eye." Seronegative by the ELISA and conventional WB tests, and having no "flu-like symptoms," Mrs. W was not considered by specialists to have a treatable tick-borne disease (TBD) until 1997 when chronic neuroborreliosis with multi-system Lyme involvement was diagnosed clinically by her family doctor. Among many symptoms were profound sense of coldness, entire bodily weakness and generalized, painful, severe muscular spasms, cardiac laboring and arrhythmias, waves of painful aural, visual, and touch hypersensitivities, aphonia, a maxillary bone-gum fistula, bradypnea, impatience, multiple sclerosis-like neurological symptoms, chills, and losses of visual acuity. Ocular examination showed a punctate retinal hemorrhage. She appeared on the verge of imminent collapse. Babesiosis originally was not a suspected co-infection.

Mrs. W's intensive, 8 months' treatment with intravenous (IV) medications—ceftriaxone followed by IV cefotaxime for treatment of the persistently severe late-stage neuro-LYD symptoms, led to a steady improvement. Attempts to truncate treatment resulted in memory losses and return of muscle pain. She also had received doxycycline 100 mg three times daily for newly resurgent Human Monocytic Ehrlichiosis. Her neurological symptoms, restless legs syndrome, cardiac laboring, unrelenting muscle pains, and generalized weakness slowly lessened but recurred with each attempt to discontinue antibiotics.

Gradual relief continued until January 1998 when treatment for LYD suddenly appeared to falter. While still on IV cefotaxime, symptoms intensified with multiple daily waves of skin flushing, sweating, cardiac arrhythmias, pricking, burning, or searing cutaneous pains, weakness, chills, painful muscle spasms, generalized itching, severe hyperacusis, blurred vision, parched lips, impatience, irritability, clumsiness, insomnia, and exquisite hypersensitivity to touch. Episodic scalp and facial sweating occurred in waves with concomitant late afternoon malaise and episodic chills.

IFA blood tests for *Babesia* then revealed a high titer of 1:512 (BBI). However, Mrs. W was afebrile, with subnormal oral temperatures (7) usually ranging from 95.7 to 97.0º F Historically, the patient had experienced unexplained blood losses during 2 otherwise uneventful elective surgeries, one preceding and one following this crisis time by several years, although other routine hemograms were consistently normal. Oral iron (300-600 mg/day) restored her postoperative Hgb from 8% to 14.5% each occasion but did not stop profound malaise and episodic chilliness.

Overview of the wife's laboratory findings and treatment of babesiosis

Mrs. W's initial *Babesia* antibody test, negative (1/05/98), was first done many months after IV and oral treatments, including azithromycin, were started to treat her chronic neuroborreliosis (July 1997). She still was being treated for both LYD and ehrlichiosis and symptoms from these were resolving slowly when daily waves of malaise dramatically escalated, incapacitating her in her 8th month of IV antibiotic treatment. Babesiosis was reconsidered diagnostically.

On 3/26/98, IFA tests for *B microti* done at BBI Laboratory revealed the above-mentioned strongly positive babesiosis titer. *Babesia* PCR blood DNA testing also was positive a year later (March 1999, IGeneX Laboratory), following partial treatment with atovaquone and azithromycin for her newly recognized chronic babesiosis.(8,9) Thus, three independent laboratories confirmed positive testing for *B microti*. In addition, a Fluorescent in situ Hybridization (FISH) test (IGeneX) was positive for fluorescing merozoite ring forms of *Babesia* piroplasms. MDL Lab also found Mrs. W's PCR test for Lyme DNA positive (11/8/99). Of additional interest, when the 2 other known diseases were diminished by treatment, there was a return of a variety of symptoms. Ehrlichiosis antibody (HME IgM) titers were then found to have risen to 1:160 (November 1999, IGeneX Lab). Symptomatic relief followed re-treatment with doxycycline. In April 2001, Mrs. W again had evidence of babesiosis via a positive *B microti* WB (MDL). Her Lyme tests now showed 3 significant positive bands on the IgM WB—a known marker for *chronic* as well as acute LYD. (10)

Interpretation of Mrs. W's Experience

Intensive treatment for babesiosis and Lyme disease over the span of 4 years returned a handicapped Mrs. W to much improved capacity. However, her life still has to be managed around 2–9 milder daily waves of likely *Babesia*-provoked symptoms. Chills subsided *temporarily* when atavoquone and zithromycin were prescribed. Later, as with her husband, a nasopharyngeal culture was positive for the newly discovered neurotoxin-former, methicillin-resistant, coagulase negative *Staphylococcus epidermidis* that had contributed to her discomfort prior to its specific antibiotic treatment.(6)

Summary of Both Cases

Mr. and Mrs. W, both of whom have documented cases of chronic tick-borne illnesses, including babesiosis, have lived in Pennsylvania most of their lives. Lesions appeared after gardening in their wooded, deer-populated, backyard north of Philadelphia. Neither spouse has been re-exposed to ticks.

Both partners have had normal MRIs. However, single-photon emission computed tomography (SPECT) scans of their brains revealed "global heterogeneous hypoperfusion" compatible with impact of noxious influences upon cerebral circulation, cited by the radiologist as likely related to the LYD of each.(11) For one partner microscopically fluorescing intra-erythrocytic parasites were found in 3 widely spaced evaluations. Neither mate had the acute babesia signs of splenic enlargement or severe hypotension.(12) They were not tested for urinary hemolysis until after atavoquone treatment (13) when these tests were negative. Diagnoses of babesiosis eventually helped to partially explain the inability of both patients to recover fully despite intensive treatment for LYD. Treatment then, for *B microti* infection, sufficiently restored both partners so that they can pursue physical and cognitive activities, although neither is asymptomatic or fully recovered.

Conclusions

Lack of general medical awareness of the presence, persistence, and severity of these widely epidemic and backyard-located, spirochetal, rickettsial and protozoan infections caused significant delay in the treatment of this couple. The delay prolonged their illnesses resulting in severe discomfort and long-term disabilities. Early recognition and medical intervention could have prevented much of the ultimate persistence of their infections.(14)

Official recording of *all* vector-borne illnesses in humans needs to be instituted, in order to bring to universal awareness the true scope of the epidemic and the necessity of proper differentiation and treatment of such infections as Lyme disease, ehrlichiosis, and babesiosis.

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