PRESENTATION SATURDAY 10, 1999

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Update from the NEMC/NYMC Extramural Chronic Lyme Study

Arthur Weinstein, M.D.

No abstract available.

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Update from the NIH Intramural Chronic Lyme Disease Study

Adriana R. Marques, M.D.

The mechanism(s) underlying persistent signs and symptoms of disease, despite the administration of what is currently considered to be adequate antibiotic therapy, is one of the most pressing and controversial issues regarding Lyme disease today. Our clinical protocol is designed to study the cause of persistent symptoms in patients with Lyme disease, and the interactions between the *Borrelia burgdorferi* and the immune system. The protocol permits us to assemble a well-characterized cohort of patients with presumed chronic Lyme disease and relevant controls, including asymptomatic seropositive controls; volunteers who have recovered from Lyme disease; patients with multiple sclerosis; and healthy volunteers. These patients are being extensively evaluated in a cross-sectional study. Patients who are found to have laboratory markers of persistent infection by study criteria are offered treatment with intravenous ceftriaxone, and followed prospectively over the course of one year. At this point, we have enrolled and evaluated 45 patients and controls in this protocol. The protocol has served as the basis for multiple parallel lines of investigation that are being developed in collaboration with scientists both inside and outside the NIH. Lines of investigation include evaluation of both currently available test for the diagnosis of *B. burgdorferi* infection and development of new approaches to assess persistence of infection in our cohort, as well as studies of possible autoimmune mechanisms involved in chronicity of the disease.

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Chronic Fatigue Syndrome and Post Lyme Disease

Lauren Krupp, M.D.

Objective: 1) To compare clinical findings in Post Lyme Syndrome, Chronic Fatigue Syndrome and Recovered Lyme.

2) To provide an update of the NIH STPO-LD treatment study.

Methods: Self-report fatigue and mood measures, psychiatric interviews, cognitive testing in PLS (n=40), CFS (n=25), recovered Lyme (N=14).

Results: 84% of PLS meet criteria for CFS. However, mild-moderate cognitive deficits are present in both groups, but are more prominent in PLS. PLS and CFS have an elevated lifetime prevalence of psychiatric disorders compared to recovered Lyme patients.

The initial 40 subjects enrolled in the STOP-LD double blind placebo controlled clinical trial show clinical findings similar to other PLS groups studied. 80% have EM and 20% have late manifestations without EM. 57% had a lifetime history of psychiatric disorder. 63% had mild or moderate cognitive impairment.

Conclusion: The clinical trial should provide important data on treatment approaches for this persistently symptomatic patient group.

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Ziracin: A Novel Antibiotic against *Bb*

Charles S. Pavia, Ph.D.

A novel antibiotic, ziracin, was tested for its ability to inhibit growth, in vitro, of the Lyme disease spirochete *B. burgdorferi* (Bb) and to cure C3H mice of an acute Bb infection. For the in vitro experiments, the MICs (based on ≥90% growth inhibition) and the MBCs (100% killing) for ziracin were compared with those for penicillin (Pen) and ceftriaxone (Ctx). Selected Bb strains (3 reference strains: B31, 297 and CA287; and 27 recent patient isolates) were cultured in a micro-dilution system in the presence of various concentrations of the 3 antibiotics. Each test well of a microtiter plate contained one-half of one million Bb, with or without antibiotic, in a final volume of 0.2 ml of BSK media. The antibiotics were diluted in BSK media and added at various concentrations (0.01-10.0 µg/ml). After incubating the sealed plates at 35-37°C for 24-48 hours, MICs were determined based on direct microscopic counts of the number of live, motile Bb visualized using phase-contrast microscopy. An MBA was considered to be the lowest concentration of antibiotic in which no bacteria survived or could be detected following subculture. This was done by taking Bb micro-cultures that had been inhibited by ≥90% (based on MIC test results), and then adding these into separate culture tubes containing fresh BSK support media lacking any antibiotics. These culture tubes were incubated for up to one week and subsequently analyzed for any growth based on microscopic observations. Our results showed that for both the Bb reference strains and the patient isolates, the MICs ranged from 0.1-0.5 µg of ziracin per mil, 0.5-2.0 µg of Pen per mil, and 0.1-.25 µg of Ctx per ml. For these same Bb strains, the MBCs (in µg/ml) for ziracin ranged mostly from 0.2-0.5, for Pen the range was 1.0-4.0, and for Ctx it was 0.2-0.5. For the in vivo studies, separate groups of C3H mice were infected intradermally with 100.00 Bb. Seven to 10 days later, mice were given daily doses of ziracin (50 mg/kg/bw) i.p., for 5 days. The treated mice were sacrificed 2 days later and extract cultures of their urinary bladders were prepared in BSK media. No Bb organisms grew out of these extract cultures, whereas Bb was isolated from extract cultures of matched, infected control mice not treated with ziracin. These data suggest that ziracin may be a possible therapy for Lyme disease since it has better or nearly equal in vitro and in vivo inhibitory activity against Bb relative to two other antibiotics that are frequently used for the treatment of Lyme disease.

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The Role of Cognitive Remediation in Brain Injured Patients and its Potential Relevance to Chronic Lyme Encephalopathy

Leo J. Shea III, Ph.D.

Studies have demonstrated that patients with brain injury have greater rates of functional recovery when they receive systematic multimodal therapy. A major part of such a system is the application of cognitive remediation to diagnosed cognitive deficits.

The overall goal of cognitive remediation is the amelioration of acquired cognitive deficits through: an informational and educational process which commences with early diagnosis, followed by discrete and highly specific neuropsychological testing; a detailed explanation of the nature and functional impact of the neurocognitive/behavioral deficits, focused on increasing patient awareness; encouraging patient flexible/malleability to the remediation process; assisting patient learning, mastering and habituating of specific compensatory strategies to improve daily functioning; increasing patient acceptance of the changes occasioned by the illness and valuing the "present self".

Initial cases studies with Lyme Disease patients indicate that, as with other acquired brain injured patients, systematic application of cognitive remediation process holds promise for increased daily functioning.

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Chronic Lyme Disease

Kenneth Liegner, M.D., P.C.

1) Thorough evaluation to confirm diagnosis of chronic Lyme disease and assess for possible additional conditions (including co-infections) which may interfere with response to treatment and recovery.

2) Antibiotic therapy is mainstay of treatment. Simplest, safest and least expensive regiment **that works**, is preferred.

3) Intravenous antibiotic therapy usually reserved for patients not responding to intensive oral antibiotics. Most patients requiring intravenous antibiotics, and particularly requiring prolonged intravenous therapy, have neurolgic involvement.

4) Duration of treatment determined by clinical response.

5) Improved methods of treatment for chronic Lyme disease are needed.

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The New Lyme Disease

Joseph J. Burrascano, Jr., M.D.

I propose we redefine what we have been calling Lyme. A huge body of research and clinical experience has demonstrated the nearly universal phenomenon in Lyme patients of co-infection with multiple tick-borne pathogens. Studies have shown that concurrent Borrelial and Ehrlichial and/or Babesial infections result in a change in a patient's individual clinical presentation, with different symptoms, atypical signs, decreased reliability of standard diagnostic tests, and most importantly, the unexpected creation of chronic, persistent forms of each of these infections. As time goes by, I am convinced that more pathogens will be found.

Therefore, "Lyme Disease", as we had come to know it, probably represents a mixed infection. This may explain the discrepancy between laboratory study of pure Borrelia infections, and what front line physicians have been seeing for years in real patients.

It is still early in our efforts to sort out clinical features of the individual pathogens in the co-infected patient, but trends are emerging. We need a better understanding of the pathogenesis of these illnesses in the mammalian host, how they interact in a co-infected host, and better diagnostic tools that include direct detection of all potential tick-borne microbes.

I propose we refer to the general clinical symptom complex as "Lyme Disease", and name the separate entities as Lyme Borreliosis (LB) Babesial infections as "Piroplasmosis" and the Ehrlichia species as "Ehrlichiosis"

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Chronic Lyme Disease: A Symptom Complex of Multiple Co-Infections: New Diagnostic & Treatment Protocols

Richard I. Horowitz, M.D.

Background: Chronic Lyme disease must be seen in the light of multiple tick borne diseases, including HME, HGE, and Babesiosis. New diagnostic and treatment protocols may effectively help patients with chronic ongoing.

Diagnosis: Lyme disease is primarily a clinical diagnosis. A 38 question questionnaire (Burrascano '95) is routinely administered to patients on initial screening. Specific attention is paid to the gestalt of symptoms including fatigue, headaches, stiff neck, migratory arthralgias and paresthesias that come and go, neuro-cognitive difficulties, and new psychiatric disturbances. Initial testing includes a Lyme Elisa, IgM & IgG Western Blot, HME, HGE & Babesiosis testing by IFA, with CBC, SMA24, TFT's, B12-folate-MMA + homocysteine testing if neuro-cognitive defects exist, and a ESR, ANA and RF depending on clinical circumstances. Diagnosis depends upon the gestalt of clinical symptoms, supported by positive antibody testing. Presumptive evidence of a tick borne disorder is made if any of the above antibody tests are low level positive, specially if the 23, 31, 34, 39 +93 bands are present on the Western Blot. Difficult diagnostic cases have Lyme urine antigen testing, Lyme multiplex PCR testing, and Babesia PCR + RNA analysis done through Igenex laboratories, Palo Alto, California. A clinical trial of antibiotics for presumptive Lyme disease yielding a Jarish-Herxheimer reaction helps to confirm the diagnosis.

Treatment: All of the 3 major tick borne illnesses are addressed with combination therapy employed to both target intracellular pathogenicity and prevent resistance. Antibiotics are rotated according to their clinical effectiveness, and include Amoxicillin and Probenecid, Ceftin, Suprax, and Doxycycline or Minocycline, in combination with a macrolide (Clarithromycin or Azithromycin). Patients are evaluated monthly and given a % of normal, reviewing initial symptoms. For symptom plateau or worsening symptoms, higher doses of antibiotics or switching regimens is helpful. Bicillin is a useful alternative to failed oral regimens, or in severely ill patients. IV medication is used as a last resort unless severe neurological defects or 3rd degree heart block exists at the onset. A new treatment protocol effective in resistant cases of Lyme disease is the use of Metronidazole for several months duration. Although Jarish-Herxheimer flares are frequent initially, many patients have shown clinical improvement within the 1st several weeks including decreased fatigue, arthralgias, and neuro-cognitive defects. Plaquenil is added for resistant arthritis or in patients with a positive ANA and evidence of immune hyper-reactivity. Treatment for Babesiosis has also become an important element in curing chronic disease in the upper Hudson Valley, NY, as co-infection rates are high. A full diagnostic work up for Babesiosis including IFA/PCR and RNA analysis is essential in chronic patients as smears are often negative.

Although Cleocin + Quinine and the newer regimen of Mepron + Zithromax may be helpful, relapse rates are high and new data has shown that the addition of high dose trimethoprim-sulfamethoxazole is extremely beneficial in elimination parasitemia. All patients are placed on sugar free yeast free diets with probiotics to prevent yeast overgrowth, with vitamin mineral supplementation. All Lyme treatment regimens are continued until the patient is 2 months symptom free.

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Treatment Roundtable

No Abstract Available

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