DISSEMINATED LYME DISEASE

DISSEMINATION

- Movement from site of entry to remote sites in body
- Method - hematogenous, lymphatics, or direct invasion along tissue planes
- Plasminogen activation may facilitate direct tissue plane invasion
- Minimum time to dissemination unclear - maybe within days of EM rash
- Early dissemination may set stage for chronicity w/ consititutional and multi-system symptomatology and late organ system involvement
- Intracellularity demonstrated in vitro. May explain chronicity and refractoriness to antibiotic therapy.

DISSEMINATED LYME DISEASE

DIAGNOSTIC CONSIDERATIONS

- CDC emphasizes LD is a CLINICAL DIAGNOSIS; lab data supportive only
- Spectrum of illness - expanding, limits of clinical manifestations unknown, need for open-mindedness
- Correct diagnosis requires good understanding of LD and basic medical knowledge because of broad differential diagnosis of LD and its many manifestations
- Detailed geographic history crucial - most people have epidemiologic exposure to ticks sometime in life: residence or travel, vacation / vocation / avocation
- Inoculum size may make a difference
  - Minimun size to result in infection is unknown
  - Low inoculum - may take months to years to attain body burden of infection sufficient to cause clinically evident symptomatology
  - During the time from first sign to diagnosis, which may be years, direct and immune-mediated injury may result

DISSEMINATED LYME DISEASE

DIAGNOSTIC CONSIDERATIONS

- Constitutional complaints w/ multi-system symptomatology, although nonspecific, may be characteristic
  - Fatigue
  - Arthralgia & myalgia , often migratory
  - Cervicalgia
  - Recurring low grade fevers
  - Night or day sweats
  - Recurring sore throat & swollen glands
  - Paresthesias
  - Sleep disturbance
  - Enthesitis
  - Panic attacks
  - Anxiety
  - Cognitive difficulties
  - Mood disturbances
  - A "sick" feeling, malaise
  - Often cyclic with 4-6 wks cycles

DISSEMINATED LYME DISEASE

DIAGNOSTIC CONSIDERATIONS

- Often look "well" may exhibit few physical findings, w/ a blizzard of symptoms that can overwhelm a physician
- Psychosomatic - Multiple patients w/ proved disseminated LD report nearly identical phenomena
- Occasionally isolated symptom or organ involvement, lacking the multi-system "flavor"

DISSEMINATED LYME DISEASE

ORGAN SYSTEMS

• CENTRAL NERVOUS SYSTEM

- Brain, brain stem, and spinal cord
- Meningitis
- Meningoencephalitis
- Meningoencephalomyelitis
- Myelopathies
- Transverse myelitis
- Hemiparesis
- Paraparesis
- Spastic para- and tetraparesis
- Motor neurone disease
- Extrapyramidal syndromes / choreiform syndromes
- "Locked-in" state
- Coma
- Progressive leukoencephalopathies
- Multiple sclerosis-like syndromes
- Seizure disorders
- Cerebral atrophy
- Organic brain syndromes / dementia
- Encephalopathy
- Neuropsychiatric syndromes; psychoses; OCD; depression; mania; bipolar disorders; other psychiatric syndromes
- Cranial nerve palsies involving any CN, multiple CN's may be involved
- Radiculoneuritides
- Sciatica-like syndromes
- Neurogenic bladder

DISSEMINATED LYME DISEASE

ORGAN SYSTEMS

• PERIPHERAL NERVOUS SYSTEM
  - Peripheral neuropathies
  - Motor / sensory / plexopathies
  - Paresthesias / dysesthesias

• AUTONOMIC NERVOUS SYSTEM DYSFUNCTION
  - Cardiogenic syncope and vasodepressor syncope
  - Abdominal bloating and abnormal peristalsis

DISSEMINATED LYME DISEASE

ORGAN SYSTEMS

- AUDITORY & VESTIBULAR APPARATUS
  - Tinnitus
  - Disturbances of balance
  - Vertigo
  - Hyperacusis
  - Hearing loss
- OCULAR - all levels, all structures of eye may be involved
  - Conjunctivitis
  - Keratitis
  - Uveitis
  - Optic neuritis
  - Retinitis / retinal vasculitis
  - Cataract formation
  - Retrobulbar myositis
  - Optic cortex cerebritis

DISSEMINATED LYME DISEASE

ORGAN SYSTEMS

- MUSCULOSKELETAL
  - Arthralgia
  - Arthritis / synovitis
  - Myositis / myopathy
  - Painful myalgia / fibromyalgia-like syndrome
  - Muscle fasciculation
  - Fasciitis
  - Enthesitis
- GENITOURINARY
  - Neurogenic bladder
  - "interstitial cystitis"
  - Renal damage / glomerulonephritis (reported in dogs only)
- ENDOCINE
  - Thyroiditis?
  - Effects on libido
  - Central hypothalamic?
  - Orchitis
  - Cyclic flare of symptoms temporally related to menstrual cycle

DISSEMINATED LYME DISEASE

ORGAN SYSTEMS

- CARDIAC
  - Dysrhythmias
  - Heart block
  - Various types of extra-systoles
  - Autonomic dysfunction; cardiogenic syncope, vasodepressor syncope
  - Cardiomyopathy; congestive heart failure
  - Myopericarditis
- GASTROINTESTINAL
  - Bloating
  - GERD?
  - Irritable bowel / colitic presentations?
  - Myoenteric autonomic dysfunction?
  - Abdominal pain / cramping esp. in children
  - Lyme hepatitis
  - Lyme enterocolitis?

DISSEMINATED LYME DISEASE

DIFFERENTIAL DIAGNOSIS

- Multi-system involvement - not too many things cause this
  e.g. joint & neurologic
  - CTD's
  - Syphilis
  - Sarcoidosis
  - Chronic viral infections (hepatitis, HIV / CMV / parvovirus)
  - TB
  - Brucellosis
  - Relapsing fever
  - Parasitic disease
- Mimicking other multi-system and autoimmune diatheses
  - RA-like w/ incr. RF; often RF decreases w/ antibiotic Rx
  - Lupus-like w/ incr. ANA, Anti-DS DNA AB; incr. C1Q I.C.'s etc.
  - Serositis/ pericarditis / thyroiditis/ etc. markers may diminish w/ ABx Rx
  - Chronic Fatique Syndrome
  - Idiopathic fibromyalgia

DISSEMINATED LYME DISEASE

LABORATORY DIAGNOSIS

- ELISA & Western Blot
  - Over-emphasis on "false positive" ELISA's
  - Is Late LD/ Disseminated LD invariably seropositive?
  - Seronegativity - Real or Bogus?
    Bb culture positive in seronegative patients
  - Study in 1996 (Kochevar & Liegner)
    16% pts had + ELISA and + Western Blot
    21% pts had - ELISA and fully diagnostic IgG or IgM Western Blots
    Many others had suspicious WB's having less than 5/10
    "CDC-specific" bands
  - Always request reporting ALL bands on a Lyme Western blot

DISSEMINATED LYME DISEASE

USEFUL LABORATORY TESTS

- ESR
- C-Reactive Protein
- CBC w/ differential
- Chemistry profile
- ANA
- FTA-ABS, if +, MHA-TP
- TFT's w/ TSH
- Angiotensin-1-converting enzyme
- Anticardiolipin antibodies
- Quantitative immunoglobulins (freq. polyclonal IgM elevation, occas. IgG incr.)
- Histologic demonstration by silver staining in biopsies/tissues removed at surgery; role for electron microscopy (glutaraldehyde fixed)
- Research assays - PCR, Lyme Urine Antigen (LUAT), Immobilization, Lyme-specific immune complexes, ELISA-capture OspA & Osp B antigen detection CSF
- Direct culture BSK-II

DISSEMINATED LYME DISEASE

USEFUL LABORATORY TESTS

- CSF examination
  - Paired LD Elisa's and paired Western blot's in serum and CSF
  - Multiple sclerosis panel
  - Cytology
  - Cell count and differential, glucose and protein
  - VDRL
  - CSF viral culture and if appropriate, viral titres
  - PCR for detection of *Bb*-specific DNA
  - OspA &/or OspB antigen detection
  - Collect ample CSF so excess can be frozen (non-cycling freezer) for future study
- Adjunctive diagnostic studies
  - MRI
  - Brain SPECT
  - Detailed neuropsychological testing
  - NCS / EMG's

DISSEMINATED LYME DISEASE

APPROACH TO TREATMENT

- Cookbook approach inappropriate
- Duration of treatment based on clinical response
- Many times trial of oral RX appropriate before resorting to IV, even with disseminated LD
- Careful periodic assessment of pt. by physician essential
- Several months of treatment may be nec. to assess response to Rx
- Full discussion of risk/benefits of treatment
- Careful periodic monitoring of pt. is nec. to detect any adverse consequence of antibiotic therapy. - CBC, chem, U/A usu. monthly to quarterly depending on agent
- Attention to gut hygiene w/ acidophilus 2 hr. following oral antibiotic dosage
- Anticipate & deal w/ complications e.g. *C. difficile*, etc. yeast overgrowth

DISSEMINATED LYME DISEASE

ORAL ANTIBIOTIC THERAPY
Monotherapy

- Tetracycline Class
  - tetracycline (TCN) 500 TID
  - doxycycline (DCN) 100 - 200 mg. Q 12 hr
  - minocycline (MNCN) 50 - 100 mg. Q 12 hr
- Amoxicillin .5 - 2 grams TID w/ or w/out probenicid
- Cefuroxime (Ceftin) 500 - 1000 mg. Q 12 hr
- Azalide Class
  - clarithromycin (Biaxin) 500 - 1000 mg. Q 12 hr
  - azithromycin (Zithromax) 250 - 500 mg. Q 12 hr

DISSEMINATED LYME DISEASE

ORAL ANTIBIOTIC THERAPY

Combination Therapy

- amoxicillin + TCN, DCN, or MNCN
- amoxicillin + an azalide
- cefuroxime + a TCN class or azalide class agent

DISSEMINATED LYME DISEASE

INTRAVENOUS RX:

Monotherapy

- ceftriaxone (Rocephin) 2 QD
- cefotaxime (Claforan) 6 grams/day
- imipenem / cilastatin (Primaxin) 250 - 1000 mg. Q 8 hr
- doxycycline 100 - 200 mg. IV Q 12 hr
- vancomycin 500 -1000 mg. IV Q 12 hr
- azithromycin (Zithromax) 500 mg. IV QD
- ampicillin 1 - 2 grams IV Q 6 hr
- penicillin G 12 - 20 million units / day

DISSEMINATED LYME DISEASE

EMPIRIC DIAGNOSTIC and THERAPEUTIC TRIAL

- Important and legitimate ole in appropriate clinical setting AFTER detailed and thorough evaluation
- Possibly even in the absence of laboratory PROOF of diagnosis
- Onus is on physician to have carefully EXCLUDED other identifiable and treatable conditions

DISSEMINATED LYME DISEASE

MONITORING OF RESPONSE TO RX

- Meticulous clinical assessment
- Patient subjective report
- Physicial examination
- Serial neuropsychological testing
- Serial Western Blots
- Serial direct antigen detection methods, particularly at time of clinical relapse
- Serial MRI's, SPECT's, NCS/EMG's
- Serial CSF examinations if perturbed parameters present initially