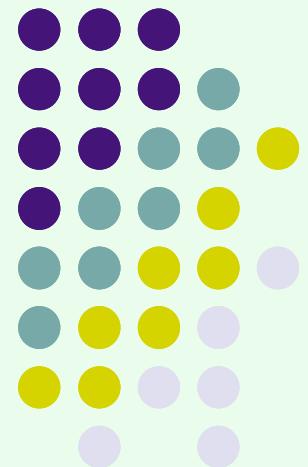


Psychiatry Grand Rounds

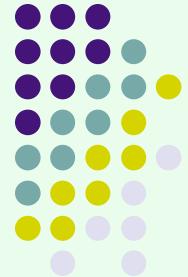
December 13, 2006



Neuropsychiatric Manifestations of Tick Borne Disease



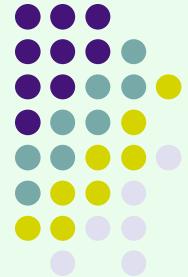
Ann F Corson MD



Infection and psychiatric illness

- “Recent immunologic, epidemiologic, microbiologic and neuropsychiatric studies point to infectious etiologies of several important neuropsychiatric disorders...several infectious diseases including human influenza virus, HIV, syphilis and Lyme disease are associated with neuropsychiatric symptoms following transmission of infectious agents to the central nervous system. ...evidence also points to potential for peri-, pre-, and postnatal infections as causes for several neurodevelopmental disorders.”

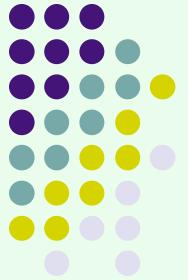
S. Hossein Fatemi, Ed., *Neuropsychiatric Disorders and Infection*
Taylor and Francis, 2005. ISBN 1 84184 520 5



Infection and chronic illness

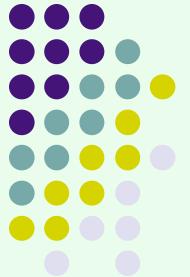
- “...infection may simply represent the first misstep along a continuum from health to long-term illness and disability.”
- “...infectious agents likely determine more cancers, immune-mediated syndromes, neurodevelopmental disorders, and other chronic conditions than currently appreciated.”
- “If a mere 5% of chronic disease is attributable to infectious agents, in the US alone 4.5 million of the 90 million people living with chronic disease might benefit from strategies designed to prevent or appropriately treat selected infections.”

O'Conner et al., Emerging Infectious Determinants of Chronic Diseases *Emerg Infect Dis* 2006; 12(7): 1051-1057



Tick bites





Our three local ticks

Dog tick *Dermacentor variabilis*

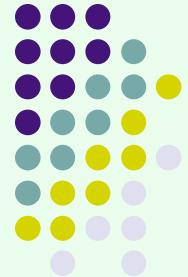


Lone star tick *Amblyomma americanum*



Deer tick *Ixodes scapularis*

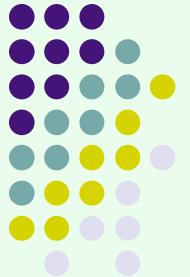




Ticks are cesspools of disease

- *Ixodes scapularis* can transmit
 - *Borrelia burgdorferi* (?others *B. garnii*, *B. afzelli*)
 - *Babesia microti* (?others WA1, MO1, *B divergens*)
 - *Anaplasma phagocytophilum* (HGA)
 - *Francisella tularensis* (tularemia)
 - *Bartonella henselae*
 - Clay, K. "Microbial Diversity in Ticks" Presentation at *7th Annual Lyme Disease Association Medical Conference*, Oct. 20, 2005, Philadelphia, PA
 - ? *Ehrlichia chaffeensis* (HME)
 - ? *Mycoplasma fermentans*
 - ? Viruses (HHV-6)

Handout: 12 references on tick contents from USA and world

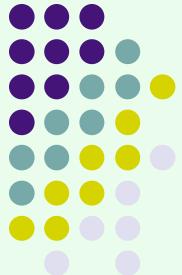


Ticks are cesspools of disease

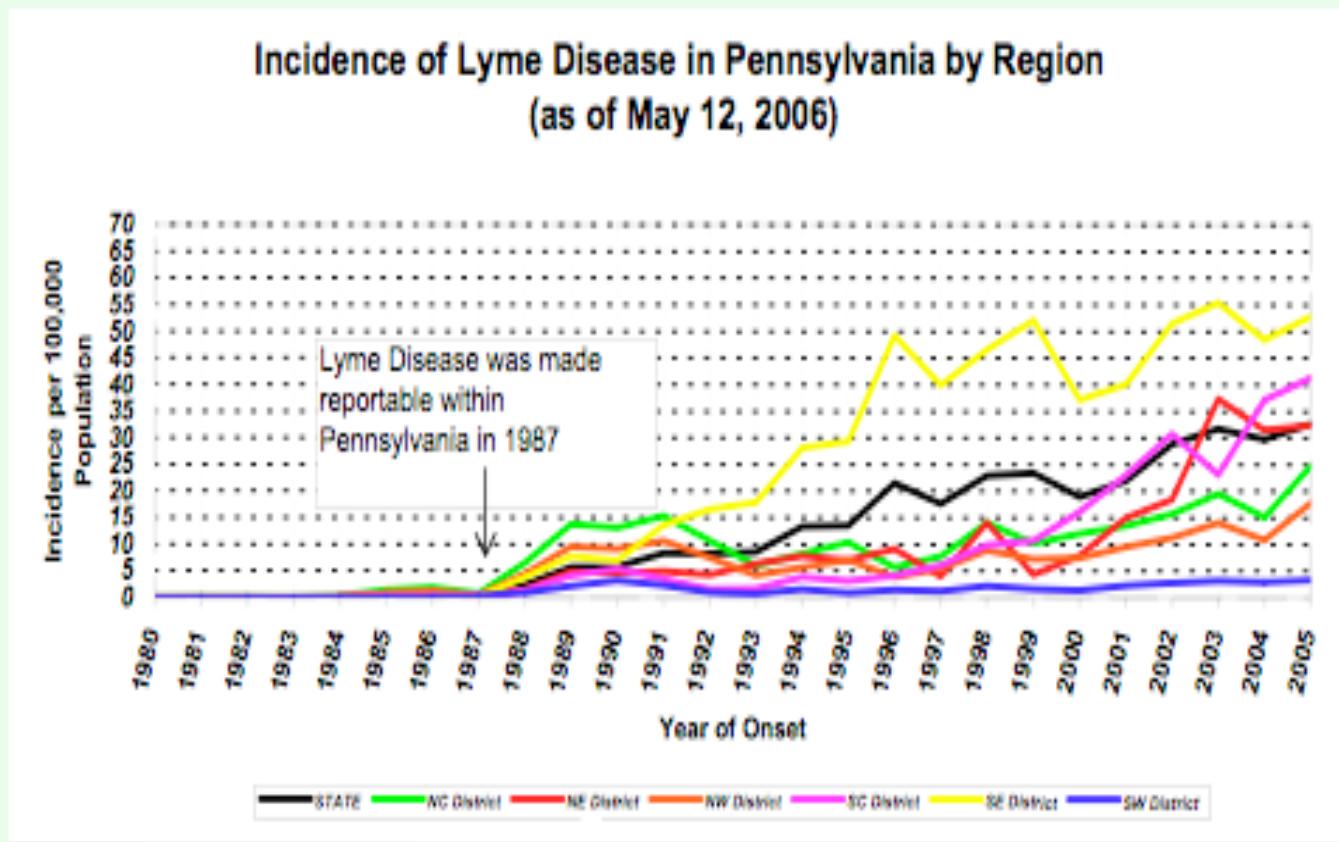
- *Amblyomma americanum* can transmit
 - *Ehrlichia chaffeensis* (HME)
 - *Borrelia lonestari*
 - *Ehrlichia ewingii*
 - ?? others
- *Dermacentor variabilis* can transmit
 - *Rickettsia rickettsiae* (RMSF)
 - *Borrelia burgdorferi* (in West Virginia)
Personal communication, Dr. Richard Dryden, May 2006
 - ?? others

ibid

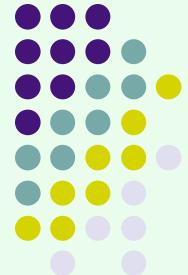
Incidence of Lyme Disease in Pennsylvania



www.dsf.health.state.pa.us/health/lib/health/lyme/LymeReportByPARegion.pdf



Local prevalence of Lyme disease



Surveys by Lyme Disease Association of Southeastern Pennsylvania (LDASEPA) www.lymepa.org

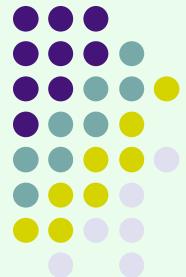
- 2004 Pocopson Township, Chester County, PA
 - 21.3% or about 1 in 5 people has/had Lyme disease
 - Infection rate of 2130/100,000
 - 10 times greater than Chester County Health Department's official count of 209/100,000

Fearn, D. et al. 2004: Population Survey in Pocopson Township, Chester County, PA Poster presentation *ILADS Scientific Program* 2004 Rye, NY.

- 2005 zip code 21921, Cecil County, MD
 - 15.6% or about 1 in 6.5 people has/had Lyme disease
 - Infection rate of 1560/100,000
 - Over 26 times greater than Cecil County's official count of 59/100,000

Hamlen R. PhD et al. 2003: Lyme Borreliosis Population Survey of a single ZIP Code in Cecil County, MD. Poster Presentation *ILADS Scientific Program* 2005, Phila, PA

Polymicrobial coinfection increases disease severity

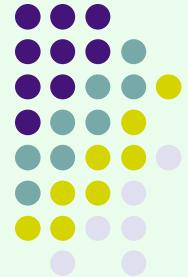


- *Babesia, Anaplasma, Bartonella*, when present with *B burgdorferi* infection
 - Increase disease severity
 - Make persistence of disease more likely
 - Synergistically suppress the host's immune system
 - Can result in debilitating neuropsychiatric symptoms

Stricker, R. et al, Lyme disease: point / counterpoint. *Expert Review of Anti-Infective Therapy* 2005; 3(2):155-165

Stricker, R. Controversies in Lyme Disease Diagnosis & Treatment. Presentation at the *International Lyme and Associated Diseases Society Annual Meeting* October 21-22, 2006. Philadelphia, PA

15 other references in handout

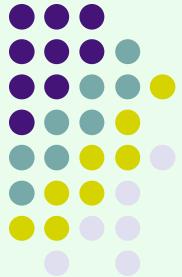


Local prevalence of coinfections

77 pediatric patients, aged 10 months to 19 years, evaluated in my practice between July 2003 and July 2005

- 80% coinfected
 - 40% two infections
 - 26% three infections
 - 9% four or more infections
- 100% had *Borrelia burgdorferi*
 - 32% *Ehrlichia chaffeensis* (HME)
 - 30% *Bartonella henselae*
 - 25% *Babesia microti*
 - 13% *Mycoplasma fermentans*
 - 9% *Anaplasma phagocytophilum* (HGA)
 - 8% had both HME and HGA

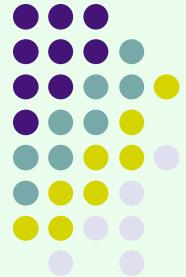
Corson, AF. A Family Doctor's Perspective on Tick-Borne Diseases In Children. *The Lyme Times Summer 2006; Children's Education Issue:* p. 3-6



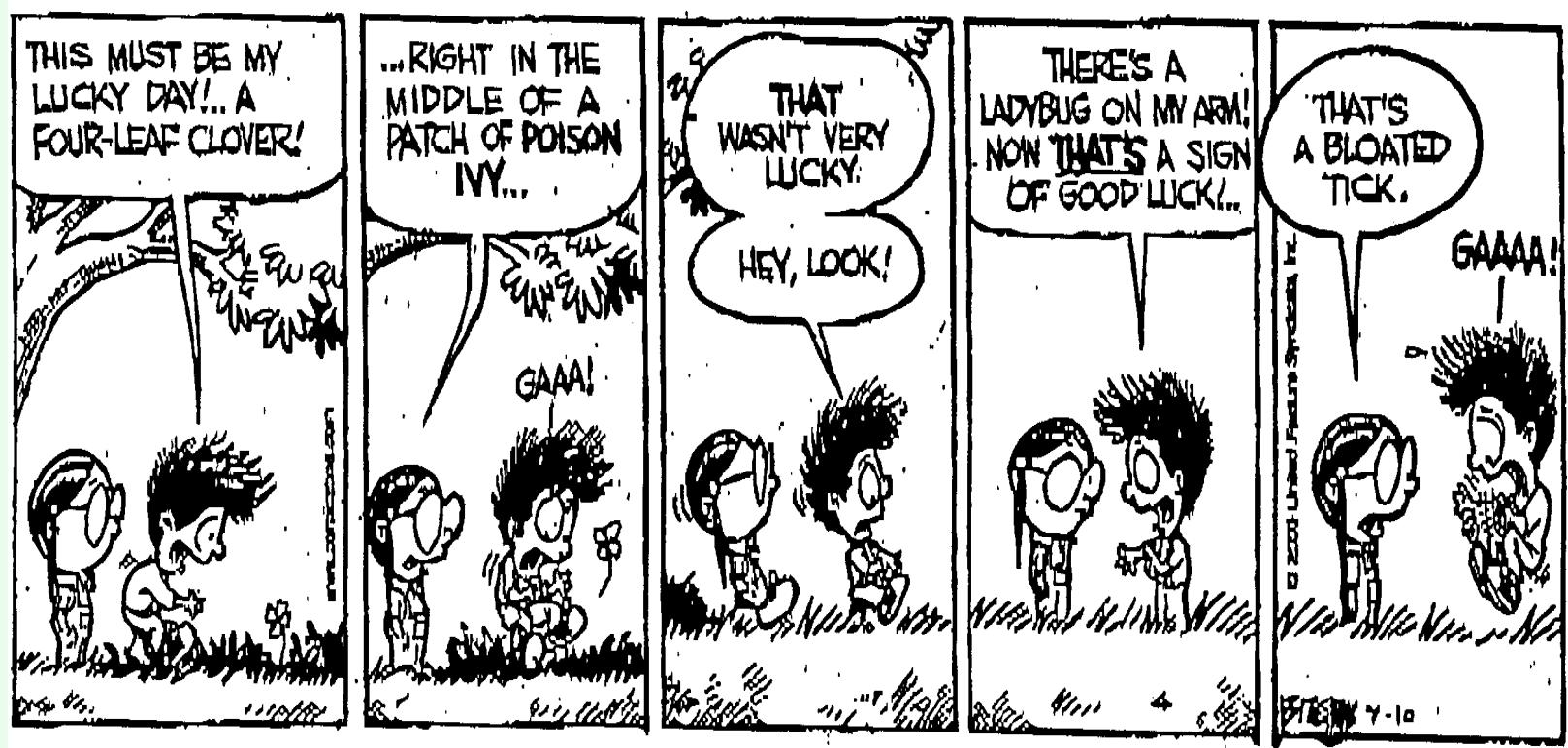
Tick populations on the rise

- Deer ticks are everywhere in PA
 - 35% increase in the deer tick population in Pennsylvania between 2004 and 2005
 - Deer ticks have spread to virtually every region of the state, even municipal parks in urban areas
- Ticks are hard to kill
 - “...we've learned that washing clothes in warm water and detergent doesn't kill all these ticks”
 - “The only sure way to get rid of them is to dry clothes on high heat for a long cycle time”
 - “without snow cover, these adult ticks can be active in temperatures as low as 28 degrees F”

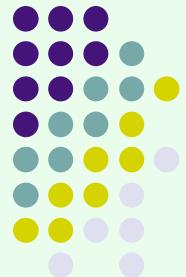
Steven Jacobs, *Penn State Agricultural Sciences News*, November 23, 2005



Tick bites are BAD luck



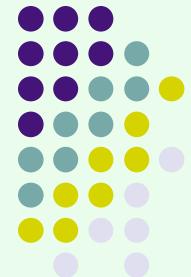
Borrelia burgdorferi pathology



- Very complex spirochete, 300 strains worldwide
- Long life cycle in many hosts, slow growing
- Evades both innate and cell mediated immune systems, kills our lymphocytes
- Hides extracellularly in immune privileged sites, penetrates many cell types to become an intracellular infection, escaping both antibiotics and host immune system
- Changes morphologically to cell wall deficient or cystic forms

27 references cited in handout

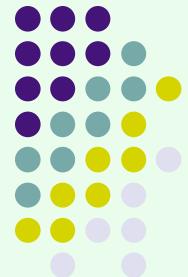
Borrelia burgdorferi neuropathology



- “...our findings demonstrate that *B burgdorferi* can disseminate to the CNS very early on in the course of the infection with little or no clinical evidence of CNS involvement.”
Luft BJ, Dattwyler RJ et al., JAMA March 11, 1992; 267(10): 1364-67
- “In a rat model, permeability changes in the blood-brain barrier begin within 12 hours after inoculation with the spirochete, and the organism may be cultured from the cerebrospinal fluid within 24 hours...”

Steere, AC in Mandell, Douglas and Bennett *Principle and Practice of Infectious Disease*, 4th edition 1995 New York: Churchill Livingstone, p. 2145

Borrelia burgdorferi neuropathology

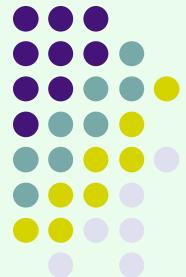


- *Borrelia burgdorferi*
 - Can bore through endothelial cells
 - Cross intracellular tight junctions
 - Has an affinity for glial cells
 - Can live inside neurons
 - Localize in or near the nucleus of neurons

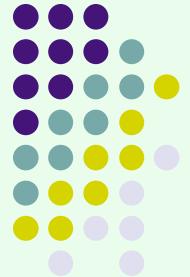
Grab, et al., *Infect Immun* 2005; 73(2): 1014-1022

Livengood and Gilmore *Microbes Infect* 2006; in press (available online at www.sciencedirect.com)

Borrelia burgdorferi consequences of infection?



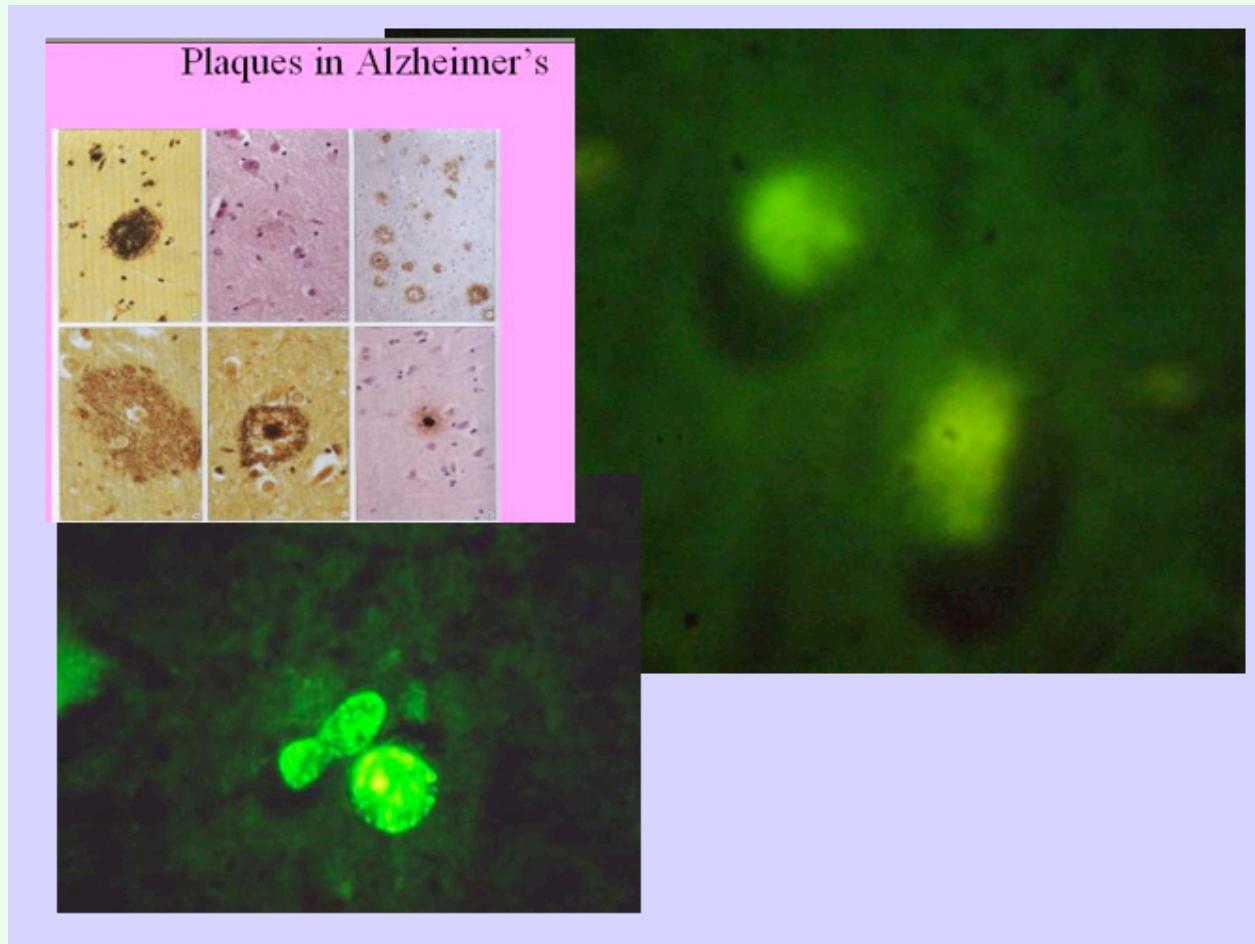
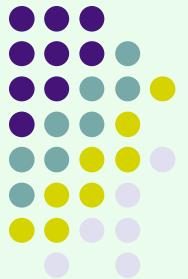
- *Bb* associated with neurodegenerative diseases
 - Multiple sclerosis
 - Brorson et al, *Infection* Dec 2001; 29(6): 315-9 2001
 - Wolfson and Talbot, *Lancet* 2002; 360: 352
 - Fritzche, *Medical Hypotheses* 2005; 64(3): 438-448
 - Motor Neuron Disease (ALS)
 - Waisbren et al., *Lancet* Aug 1987; 332-333
 - Halperin et al., *Arch Neurol* 1990; 47: 586-594
 - Harvey and Martz, *Acta Neurol Scand* 2006, in press
 - Rothstein, J., *Nature* 2005; 433, letters



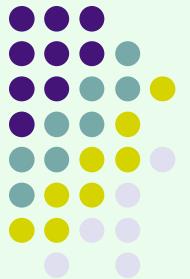
Borrelia burgdorferi consequences of infection?

- *Bb* associated with neurodegenerative diseases
 - Frontotemporal dementia
 - Dwork et al., *J Neuropsychiatry* 1995; 7(3): 345-347
 - Alzheimer's dementia
 - MacDonald & Miranda, *Human Pathology* 1987; 18: 759-761
 - Miklossy, *J. NeuroReport* 1993; 4: 841-848
 - Meer-Scherrer, *Current Microbiology* 2006 in press
 - MacDonald, *Medical Hypotheses* 2006; 67(3): 592-600

Borrelia burgdorferi consequences of infection?



Borrelia burgdorferi consequences of infection?



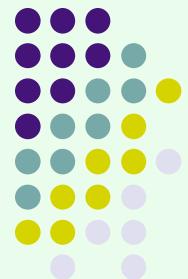
DNA in
Plaques

Only Borrelia DNA
Glow Green in the Picture

Borrelia burgdorferi Flagellin DNA , In situ hybridization, Large Plaque
1000x original magnification

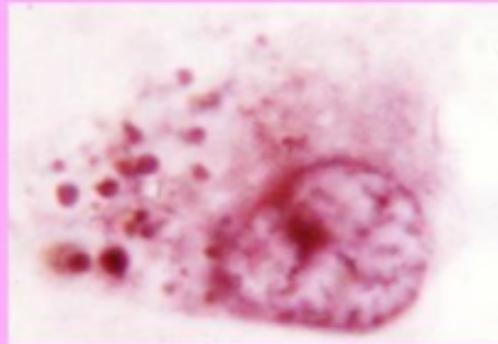
on & Love: Neuropathology 2e © 2004 Elsevier Ltd.

Borrelia burgdorferi consequences of infection?



GVB “Checklist”

Alzheimer's disease
Hippocampus
Variable in Number



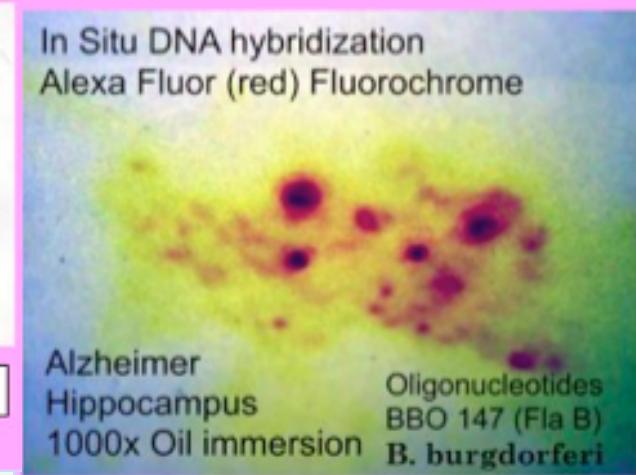
Granules vary in size ---little to big

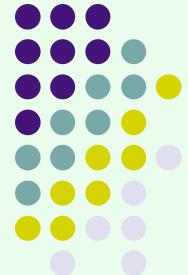
MacDonald
human Alzheimer In situ DNA

In Situ DNA hybridization
Alexa Fluor (red) Fluorochrome

Alzheimer
Hippocampus
1000x Oil immersion

Oligonucleotides
BBO 147 (Fla B)
B. burgdorferi

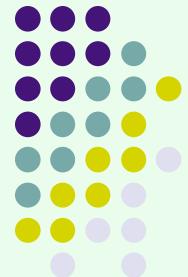




Borrelia burgdorferi consequences of infection?

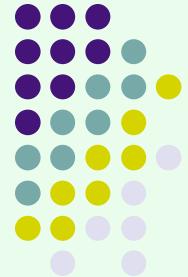
- *Borrelia burgdorferi* can be congenitally transmitted during any stage of pregnancy
- *Bb* can infect the fetus despite antibiotic treatment of the mother
 - Schlessinger, PA, Steere, AC, et al., *Annals Int Med* 1985; 103: 67-8
 - Markowitz, L., Steere, AC, et al., *JAMA* 1986; 255: 3394-6
 - Barbour, AG, et al., *Arthritis Rheumatism* 1987; 30(Suppl): S50
 - MacDonald, A., Burgdorfer, W. *NY State J Med* 1987; 87: 616
 - Weber, K., et al. *Pediatric Infectious Disease Journal*; 1988; 7(4):286-289
 - MacDonald, AB *Rheum Dis Clin North Am* 1989; 15(4): 657-677
- *Bb* found in breast milk
 - Schmidt, et al. *Diag Microbiol Infect Dis* 1995; 21(3): 121-128
- *Babesia microti* is congenitally transmitted
 - Fox, et al., *Pediatr Infect Dis J* 2006; 25(2): 169

Borrelia burgdorferi gestational borreliosis



- Gestational borreliosis associated with
 - Maternal toxemia of pregnancy, repeated miscarriages
 - Intrauterine growth retardation, congenital malformations
 - Fetal death (in utero or at term)
 - Neonatal hyperbilirubinemia, respiratory distress, sepsis and death
 - Sudden infant death syndrome within the first year of life

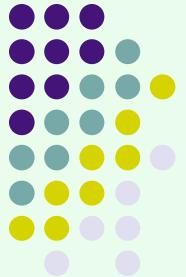
MacDonald, AB. *Rheum Dis Clin North Am* 1989; 15(4): 657-677



Signs and symptoms of TBD

- Less than half of patients remember a tick bite
Steere A Am J Epidemiol 1978; 108: 312-321
- Of those that remember a tick bite, less than half get an erythema migrans EM rash
 - EM rashes highly variable in appearance and often not recognized by patients and physician, even in endemic areas

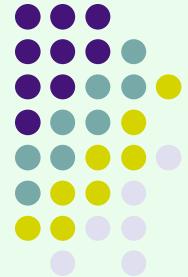
The ILADS Working Group, *Expert Rev Anti-infec Ther* 2004; 2(1): S1-S13
- *Borrelia burgdorferi* disseminates quickly to the CNS where it may remain quiescent for months to years
 - Fallon and Nields *Am J Psychiatry* 1994; 151:1571-1583
 - Fallon et al., *Psychiatr Q* 1992; 63(1): 95-117
 - www.lymeinfo.net/medical/LDSymptoms.pdf 2006 (51 pages of citations)



Signs and symptoms of TBD

- Flu-like illness at any time of year
- Fatigue, often unrelieved by rest
 - Daily energy sags, especially in mid to late afternoon
- Headache, neck pain and stiffness are very common
- Reduced or absent aerobic exercise tolerance
- Intermittent, cyclical fevers, day and/or night sweats
- Sleep disturbances, night terrors, sleep walking
- Migratory, intermittent joint pains, back aches, morning stiffness

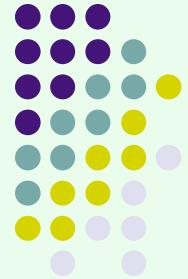
ibid



Signs and symptoms of TBD

- Myalgias of all kinds, muscle spasms, twitches, restless leg syndromes, fluctuating muscle weakness and coordination
- Excessive thirst
- Tinnitus, fluctuations in hearing, dizziness, intermittent red, hot pinnae [ears] (esp. in children)
- Dry eyes, fluctuations in vision, floaters, dark circles under the eyes
- Cyclical sore throats with or without swollen glands
- Intermittent teeth pain or sensitivities to hot, cold or sweets

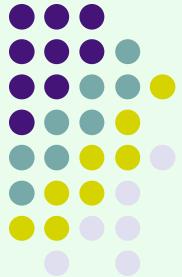
ibid



Signs and symptoms of TBD

- Palpitations, chest pains
- Shortness of breath, air hunger, dry cough
- Abdominal pains of all kinds, intermittent nausea (even vomiting), heartburn, irritable bowel symptoms, irregular bowels
- Urinary urgency and frequency, incontinence, nocturia, sudden lack of control in a toilet trained child, return to enuresis, dysuria, bladder pain and spasms, interstitial cystitis

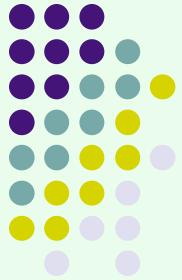
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Signs and symptoms of TBD

- Menstrual irregularities, dysmenorrhea, ovarian cysts
- Testicular pain, chronic prostatitis
- Rashes of all kinds that come and go
 - Psoriasis, atopic or neurodermatitis
 - In infants, may have a diaper rash that doesn't respond to normal treatment
- Frequent infections; either viral, bacterial or fungal
 - Chronic pharyngitis, sinusitis, bronchitis, gingivitis, stomatitis, UTIs, URIs (esp. in children)

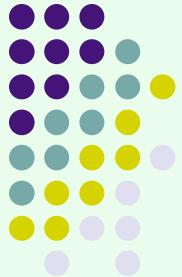
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Neurological symptoms

- Cranial neuropathies and neuralgias
 - Bell's palsy occurs in only 5-10% patients
 - Any cranial nerve can be involved (2nd, 8th, 6th or 5th)
- Spinal radiculoneuropathies
 - motor or sensory spinal radiculoneuropathies presenting with sharp stabbing shooting pains, paresthesias, weakness, fasciculations (can be excruciatingly painful)

ibid

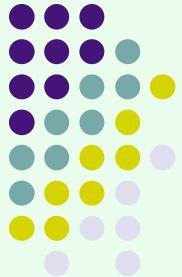


Neurological symptoms

- Peripheral neuropathies
 - Migratory sensory and motor neuropathies, especially of extremities
- Autonomic nervous system neuropathies
 - “Bell’s palsy” of the gut

Sherr, V., “Bell's Palsy of the Gut” and Other GI Manifestations of Lyme and Associated Diseases *Practical Gastroenterology* 2006; 30(4): 74-91
 - Neurally mediated hypotension (NMH)
 - Cardiac arrhythmias
- Pseudotumor cerebri

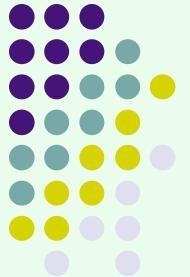
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Neurological symptoms

- Movement disorders
 - Motor or vocal tics
 - Muscle spasms, twitches, fasciculations
 - Ataxia, balance abnormalities, spastic paraparesis, cerebellar syndromes
 - Loss of developmental milestones, previously acquired motor skills, or abnormal skill development in infants and children
- Seizure disorders
 - Partial complex, absence, grand mal, hard to categorize “locked-in”, “zone-outs”, “spasmodic muscle attacks”

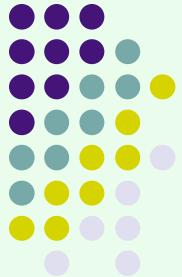
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Neurological symptoms

- Degenerative diseases of the brain and spinal cord
 - Transverse myelitis (Bannwarth's syndrome)
 - Guillan-Barre syndrome, amyotrophic lateral sclerosis (ALS)
 - Multiple sclerosis
 - Alzheimer's dementia

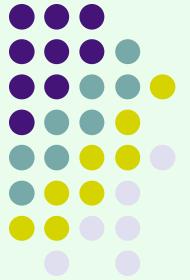
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Neuropsychiatric symptoms

- Meningitis symptoms of varying intensity
 - Headaches of all kinds (often severe) often with photophobia
 - Stiff and sore neck
- Encephalitis symptoms of varying intensity
 - Fluctuating mood disturbances with emotional lability
 - Sleep disturbances
 - Sensory hypersensitivities and general irritability
 - sound, light, odors, touch, alterations in taste and smell
 - Poor balance and coordination

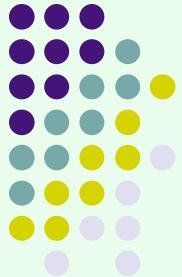
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Neuropsychiatric symptoms

- Encephalitis, cont.
 - Subtle to severe cognitive changes
 - Problems with focus and concentration
 - ADD, easy distractibility
 - 90% children have a decline in school performance
 - Short term memory difficulties
 - Poor word or name finding with slow verbal fluency
 - Dyslexia-like errors when writing or speaking
 - Deficits in auditory and visual sensory processing speeds
 - Spatial disorientation (getting lost in familiar places)
 - Acute confusional states
 - Dementia

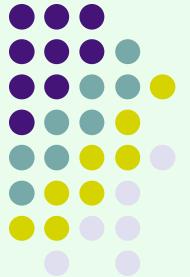
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Psychiatric symptoms

- Psychiatric symptoms can be the primary presenting symptom of new, recurrent or persistent infection
 - Social withdrawal, decreased participation in activities
 - Mood disturbances, irritability, emotional lability
 - New onset anxiety, panic attacks, or phobias
 - Affective disorders of all kinds
 - Depression (suicidal ideation)
 - Bipolar or manic-depressive disorder
 - Depersonalization

Fallon and Nields, *Am J Psychiatry* 1994; 151: 1571-1583
ibid



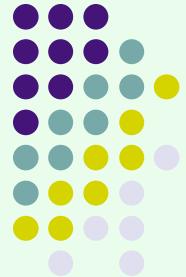
Psychiatric symptoms

- Psychiatric symptoms, cont.
 - Obsessive compulsive disorders
 - Rage attacks, anger management disorders
 - Cutting behavior, especially in adolescents
 - Oppositional disorders, personality disorders
 - Psychosis
 - Paranoia, delusions
 - Auditory, visual, olfactory and tactile hallucinations
 - Schizophrenia like syndromes
 - Substance abuse

ibid

Hess et al., *Biol Psychiatry* 1999; 45(6): 796

Fallon et al., *Psychiatric Annals* 2006; 36(2): 120-128

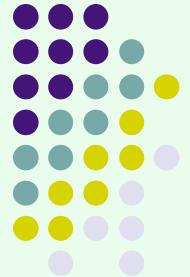


Psychiatric symptoms

- Coinfections make psychiatric symptoms worse:
 - *Babesia*
 - Anxiety, panic disorders, depression
 - *Bartonella*
 - OCD, self-mutilating behaviors
 - Seizures
 - Rage attacks
 - Psychosis - “sudden severe explosive episodes of brief, bizarre, agitated psychotic breaks in otherwise bright adolescents” Dr. V Sherr, personal communication

Joseph J Burrascano, Jr, MD *Diagnostic Hints and Treatment Guidelines for Lyme and Other Tick Borne Illnesses* 2005 15th edition

www.ilads.org/burrascano_0905.html

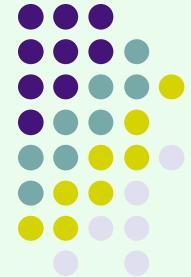


Signs and symptoms of congenital Lyme disease

- Gestational Borreliosis associated with
 - Floppiness with poor muscle tone
 - Irritability
 - Frequent fevers and illnesses early in life
 - Skin and joint sensitivities, body pain
 - Gastro esophageal reflux
 - Sleep disturbances, nightmares, sleep walking

Dr. Charles Ray Jones and Edina Gibb, Gestational Lyme Disease Case Studies of 102 Live Births. Presented at *Lyme Disease Symposium 2006 Maryland*

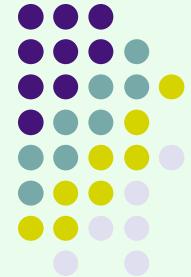
Neuropsychiatric manifestations of congenital Lyme disease



- Gestational Borreliosis associated with
 - Neurological abnormalities
 - Athetoid movement disorders, tics
 - Cranial and peripheral neuropathies
 - Developmental delays in speech or motor skills
 - Learning disabilities
 - Poor reading and writing skills, dyslexia
 - Slow sensory processing speeds
 - Autism-like syndromes

ibid

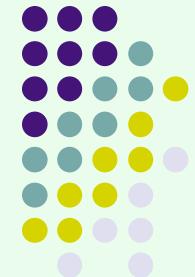
Neuropsychiatric manifestations of congenital Lyme disease



- Gestational Borreliosis associated with
 - Psychiatric abnormalities
 - ADD, hyperactivity (poor reaction to Ritalin)
 - Anxiety, phobias, panic attacks
 - Anger rages
 - Aggressive behaviors
 - OCD
 - Paranoia
 - Emotional lability and mood swings
 - Depression with suicidal ideation/attempts

ibid

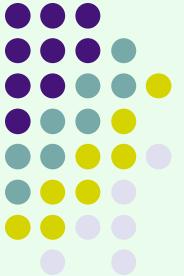
Borrelia burgdorferi antibodies in psychiatric inpatients



- 926 psychiatric inpatients in the Czech Republic found 33% had positive serologies for Bb. They concluded that, in endemic areas, a significant proportion of psychiatric inpatients may be suffering with the neuropathogenic effects of *Borrelia burgdorferi* infection

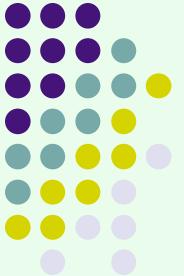
Hajek et al., Higher Prevalence of Antibodies to *Borrelia burgdorferi* in Psychiatric Patients Than in Healthy Subjects.
Am J Psychiatry 2002; 159(2): 297-301

Assessment patient history



- History of Lyme disease diagnosis
- History suspicious for EM rash
- History of tick attachment(s)
- Deer in the home, school or work environment
- Outdoor work or recreational activities in endemic region
- Travel history to endemic regions
- Presence of non-psychiatric medical disease

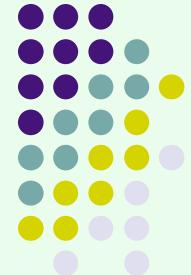
Assessment patient history



- New onset of significant psychiatric disease
 - No psychological precipitants
 - No pre-existing psychiatric disease in patient or family
- Unusual or atypical case presentation
 - First panic attack at age 50 lasting longer than 30 minutes
 - Very rapid mood fluctuating, extreme irritability
- Paradoxical reaction, poor or no response to multiple classes of psychiatric medication
- Sudden worsening of previously stable psychiatric patient

Fallon et al., *Clin Infect Dis* 1997; 25(Suppl 1): S57-63

Assessment diagnostic testing

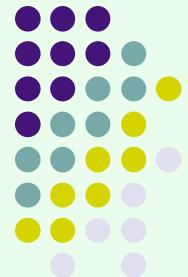


- “If false results are to be feared, it is the false negative result which holds the greatest peril for the patient.”

Alan B. MacDonald, MD

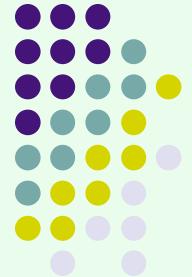
MacDonald, AB. Gestational Lyme Borreliosis:Implications for the fetus *Rheum Dis Clin North Am* 1989;15(4): 657-677

Assessment diagnostic testing



- CDC two-tiered serology ELISA with confirmatory Western Blot
 - College of American Pathologists: commercially available FDA-approved kits only 36-70% sensitive, the ELISA assay does not have adequate sensitivity to be part of a two tiered approach to diagnosis
Bakken et al., J Clin Microbiol 1997; 35(3): 537-543
 - NY Dept Health 1996: found CDC's two tiered testing missed 82% positive Lyme cases
DeBuono, B. NY Dept of Health report to CDC April 15, 1996
 - John's Hopkins study 2005: found CDC two tiered testing missed 75% of positive Lyme cases
Coulter, et al., J Clin Microbiol 2005; 43: 5080-5084

Assessment diagnostic testing



- Western Blot

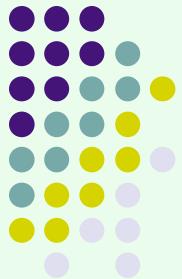
- A CDC positive Western Blot requires presence of 5 of 10 IgG and 2 of 3 IgM bands that are common to many spirochetes, not just *Bb*. Two of the most species specific bands for *Bb* (31, 34) omitted. This makes no sense.
 - Quality of commercial western blots vary widely
 - Controls for testing are made from B31 strain that bears little resemblance to wild infectious strains

Burgdorfer, W. *Infect. Immun.* 1998; 56: 1831-36

- Western Blot need only show one species-specific band to demonstrate exposure to *Bb* therefore confirming a clinical diagnosis of Lyme disease. These species-specific bands include 18, 23-25, 31, 34, 39, 83-93 kDa.

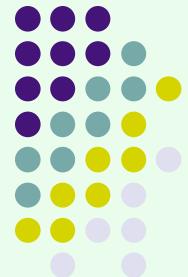
Harris, NS. *J Spirochetal Tickborne Dis* 1998; 5(1): 16-26

Assessment diagnostic testing



- Polymerase chain reaction (PCR) testing
 - More useful in tissue biopsy than in bodily fluids
 - 71% sensitivity in skin biopsies
Lebech *APMIS Suppl* 2002; 105: 1-40
 - Look for in urine, blood, serum, CSF
 - Jones, Steere et al., *J Clin Microbiol* Dec 2006; 44(12): 4407-4413
 - Fallon, *Psychiatric Annals* Feb 2006; 36(2): 120-128
 - Best from a reputable lab with good primers
- Pathological evaluation
 - Silver stains technically difficult
 - Proper microscopes expensive (dark field, EM)

Assessment diagnostic testing



- For best yield use combination of serology, PCR (and culture, if available)

Coulter et al., *J Clin Microbiol* Oct 2005; 43(10): 5080-5084

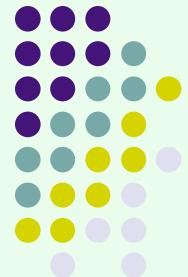
- TBD testing: best options available
 - IGeneX Laboratory in California
 - Fully accredited, Medicare credentialed, nationally licensed, including NY State

www.igenex.com

- Medical Diagnostic Laboratories (MDL) in New Jersey

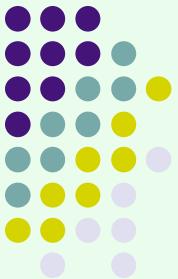
www.mdlabs.com

Assessment diagnostic evaluation



- SPECT of brain
 - Diffuse heterogenous hypoperfusion
 - Fallon et al., Clin Infect Dis 1997; 25(Suppl 1): S57-63
 - Perfusion improves after IV ceftriaxone treatment
 - Logigan, Steere, Kamplan, *J Infect Dis* 1999; 180: 377-83
 - Logigian, Steere et al., *Neurology* 1997; 49:1661-1670
- MRI of brain
 - UBOs nonspecific but sometimes resolve with treatment
- EEGs
 - normal or diffuse to discrete abnormalities

Assessment diagnostic evaluation



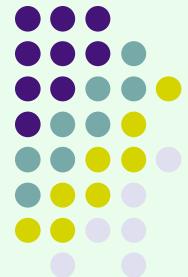
- EMG
 - Often normal to nonspecific polyneuropathy
- Cerebrospinal fluid evaluation
 - Most often completely normal
 - Intrathecal antibodies in less than 9%
 - Slightly elevated protein, slight leukocytosis
 - Rule out other diseases

Coyle, et al., *Neurology* 1995; 45: 2010-2014

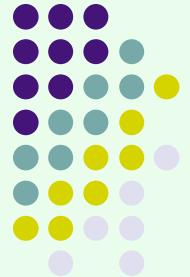
Fallon et al., *Psychiatric Annals* 2006; 36(2): 102-128

The ILADS Working Group, *Exp Rev Anti-Infect Ther* 2004; 2(1): S1-13

Assessment diagnostic evaluation



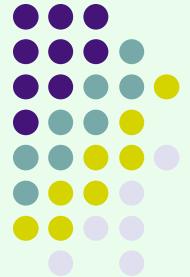
- Neuropsychological evaluation
 - Objective measure of impairment in memory, attention, concentration, verbal fluency, perceptual motor functioning and/or conceptual ability
 - Wechsler Adult Intelligence Scale (WAIS-III)
 - Wechsler Intelligence Scale for Children (WISC-III)
 - Wechsler Memory Scale (WMS-III)
 - Buschke Selective Reminding test
 - Controlled Oral Word Association test
 - Fallon et al., *Clin Infect Dis* 1997; 25(Suppl 1): S57-62
 - Tager et al, *J Neuropsychiatry Clin Neurosci* 2001; 13(4): 500-507
 - Keilp et al., *J Int Neuropsychol Soc* 2006; 12(1): 119-129



Case presentation 1

14 year old white female

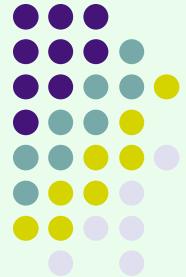
- CC: “hit a brick wall at age 9 in 1998”
- PMH: SVD without complications with normal early growth and development until age 9
- Risk factors: lives in suburban area with deer plentiful. No known tick bites. Two cats.
- HPI: started to develop sleep disturbance, separation anxiety, school phobia, progressively intensifying anxiety and depression. Her grades fell dramatically age 10-11. Subsequently underwent psychiatric hospitalization for worsening anxiety, phobia, OCD followed by enrollment in a partial program. She was still quite symptomatic with panic and anxiety on Lexapro, Klonopin and Gabitril.



Case presentation 1

14 year old white female

- ROS: recurrent fevers, fatigue, red pinnae, abdominal pain with intermittent diarrhea, AH/SOB
- Exam: 5'6 1/2" 137 lbs VS stable, afebrile, shoddy cervical lymphadenopathy, chelosis, painful spasm of CT junction, diffuse synovitis elbows, wrists, knees, ankles, slightly increased reflexes, alert, cooperative but emotional, clingy to mother
- Labs: in 2003 revealed + PCR in blood for *Borrelia burgdorferi* and *Bartonella henselae* at MDL, 5 species-specific bands on IgM WB at IGeneX and + ANA



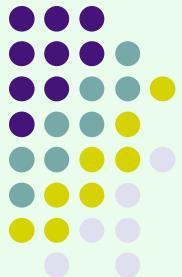
Case presentation 1

14 year old white female

- Course: treatment has brought about gradual improvement in all her symptoms. Further testing in 2005 showed new IgG for *Bh*, less reactivity on IgM WB and negative ANA
- Currently: normally behaving 17 y/o, back in normal school doing well academically, no recurrent fevers, bowels are normal, sleep is “wonderful”, energy “fantastic”, still with some synovitis of the knees and some anxiety, well controlled on Lexapro and Klonopin

Case presentation 2

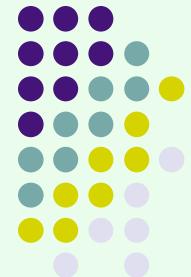
15 year old white male



- CC: psychotic depression and joint pain
- Risk factors: lots of tick bites as younger child playing in wooded lot with stream, deer on property, ticks on dog, (with Lyme diagnosis.)
- PMH: normal full term SVD with normal growth and development. Myringotomy tubes as toddler. In academically gifted program in elementary school
- HPI: age 9 1/2 developed musculoskeletal and or neuralgic pain in cervicothoracic junction and neck and awoke one morning with swollen knee. FMD found him seropositive for LD with conventional testing and treated him with three weeks of amoxicillin

Case presentation 2

15 year old white male



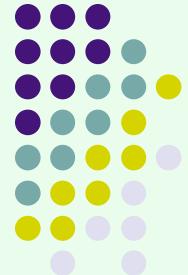
Despite treatment, he continued with intermittent knee pains.

At age 12, (March 2000) he abruptly developed encephalitis, waking up one morning in a grand mal seizure. MDs at prestigious local children's hospital were puzzled by finding serologic evidence of infection with *Bartonella henselae* in his CSF. MRI brain was normal. He was treated with 10 days of oral Bactrim and Rifampin.

By spring 2002 he became depressed but had a poor response to Zoloft.

Case presentation 2

15 year old white male



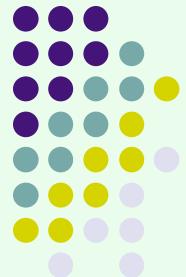
By the end of 2002, he had become suicidal and psychotic, was hospitalized after a suicide attempt and subsequently released into a partial program.

Shortly before my evaluation in October 2003, he had developed deepening depression, ADHD and increased motor agitation (leg “motor running”)

- Meds: 10/03 Zoloft, Seroquel, Strattera, Ritalin
- ROS: fatigue, orthostatic dizziness, SOB, night sweats, chills, flushing, poor balance, recurrent sore throat, fractionated sleep and a bizarre, tingling hypersensitivity to being touched electric shock like feeling, couldn't stand being touched, scalp burned when he combed hair, hyperacusis, photosensitivity

Case presentation 2

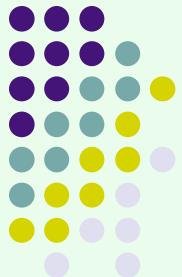
15 year old white male



- Exam: 5'9" 128 lbs, stable vital signs, afebrile, shoddy cervical lymphadenopathy, tender suboccipital region, discomfort in epigastrum, synovitis of knees and ankles, increased DRTs, touching skin of his chest made his face tingle, motor agitation of lower extremities, normal strength, gait and reflexes, flat affect, poor eye contact, sat for interview with head covered by hooded sweatshirt with downward gaze and arms folded tightly across chest
- Labs: October 2003 equiv IgG WB Bb, 3 sp sp bands on -IgM WB Bb, +IgG HGA 1:40

Case presentation 2

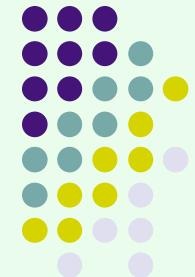
15 year old white male



- SPECT Jan 2004 mild diffuse heterogeneous hypoperfusion of both cerebral hemispheres
- Course: Pt responded well to treatment with steady improvement in all symptoms. He became more interactive with family, got his sense of humor back, started to show affection to his little sister for first time in years. Came off psych meds by March 2004. Returned to normal school fall of 2004. Sleep disturbance, dysesthesias, joint pains continue to wax and wane. By Jan 2005, had +IgG WB, 7 sp sp band on IgM WB, and new IgG Bm 1:40.
He became worse cognitively in early 2006 with poor

Case presentation 2

15 year old white male



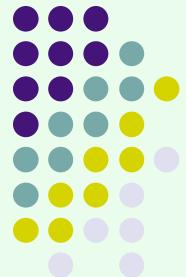
focus and concentration and return of depression. In Jan 2006 +IgM WB with 6 sp sp bands. Repeat SPECT showed only one medium area of left parietal lobe heterogeneous hypoperfusion.

New tick bite July 2006 with return of significant joint pains of elbows, wrist, knees and ankles and a decline in school performance, trouble paying attention and difficulty in math.

- Currently: after a change in treatment and the addition of Adderall by his psychiatrist, he feels better emotionally, has better energy but still complains of cyclical joint pains and abdominal pains. Tactile dysesthesias are gone. On exam, still has marked synovitis of left knee.

Case presentation 3

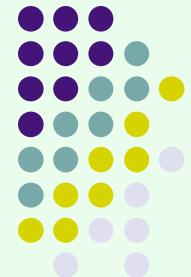
18 year old white male



- CC: brought by mother for evaluation of TBD. She states she thinks he was “born with Lyme”.
- Risk factors: lives in suburban setting with deer in yard, ticks on pets, other family members ill with TBD
- PMH/HPI: 52 hr labor at term, neonatal jaundice, colic until age 7 months, frequent URIs, development of OCD, anger and “terrible” defiant behavior age 2, but was extremely bright. He learned the alphabet by age one, knew all the states and their capitals by age two, had a “quest for naming things”, could put 200 piece jig saw puzzles together with ease as pre-schooler.

Case presentation 3

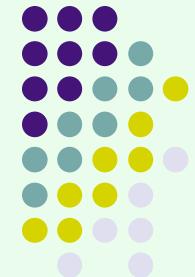
18 year old white male



Learned to read using “Hooked on Phonics” in 3 days of obsessing with it and could read 12th grade words in first grade. He could understand college level computer books at age 9-10. At age 8 his formal IQ was 170. Gross motor lagged behind as he didn’t walk until 15 months. He didn’t sleep through the night until he was medicated at age 8. Symptoms of ongoing sleep disturbance, OCD, anger and defiance along with hyperactivity continued to worsen and by age 8 he was diagnosed with severe ADHD, Asperger’s, food allergies and chemical sensitivities. He suffered frequent URIs and developed growth asymmetry of right lower jaw. He was placed in alternative schooling.

Case presentation 3

18 year old white male

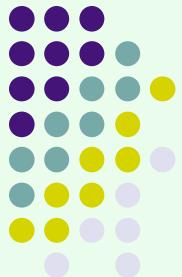


Over the years, he was treated with risperidone, Ritalin, Adderall, lithium, Catapres, clonidine. From 4th to 8th grade, he had behavioral therapy, mobile therapy and TSS in the home 52 hours a week. None of these interventions helped much. Recently, repeat IQ testing revealed a drop of 70 points to 100.

Mother found a doctor who, after finding 4 sp sp bands on IGeneX IgM WB, treated him for one year with oral antibiotics (2003-2004). His anger and sleep improved somewhat. At the age of 16, he changed to a different school setting that seemed better for him. He started his own computer business and bought his own car.

Case presentation 3

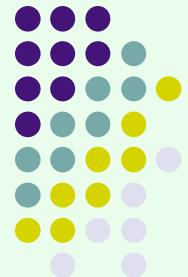
18 year old white male



- ROS: ongoing sleep disturbance, lifelong fatigue, problems with reading comprehension, memory, word finding, gets lost easily, slow to learn new information, poor balance, headaches, chronic sinus problems, red ears, joints of extremities and neck crack, is easily agitated, still gets road rage occasionally
- Exam: 6'1" 183 lbs, stable VS, afebrile. Right jaw small causing twisting of mouth and problem with speech articulation, mild suboccipital tenderness, benign abdomen, no synovitis, small sandpaper eruption both UEs extensor surfaces, normal reflexes and balance tests, normal gross motor and sensory testing, some psychomotor agitation of LEs, general agitation with

Case presentation 3

18 year old white male

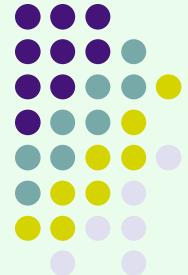


trouble sitting still, some mumbling of speech with frequent word block, recall difficulties on questioning but an appropriate, cooperative affect.

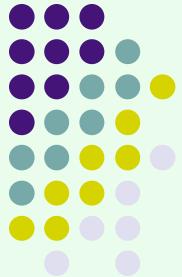
- Labs: PCR + *Bb* urine at IGeneX, only one sp sp band IgM WB, +IgG *Bh* 1:60 at Specialty Labs, +IgG HME 1:80 at Igenex. ACLA IgM and IgA were elevated
- SPECT: 10/06/06 patchy random areas of hypoperfusion abnormalities in both cerebral hemispheres
- Course: At first follow up, he had had two periods of cyclical Herxheimer reaction to antibiotic consisting of worsening brain fog, fatigue, myalgias and joint pain.

Case presentation 3

18 year old white male



Rest of ROS significant for a neck that “feels out of place”, nagging cough, binge eating, stabbing pains in muscles of thighs, increased somnolence and fatigue, and was ticketed for speeding and trying to evade police. Repeat exam revealed new synovitis of knees but overall calmer affect with less psychomotor agitation.

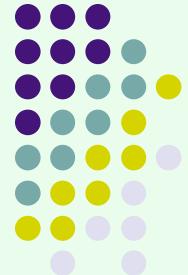


Case history new patient

- 36 year old white female's chronology of illness over the past 15 years. Patient remembered an EM rash on her thigh in high school and has lived on a farm her whole life.

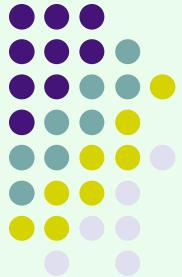
I first started with traceable symptoms in 1992 - lightheadedness, feeling like I was going to pass out, shortness of breath, heart palpitations, fatigue, numbness, trouble concentration, lower back pain and headaches. Over the years I developed anxiety/panic attacks and all sort of unexplained pains and muscle weakness. The light-headedness, back pain and fatigue became increasingly worse. I also started getting large, completely bald patches on my scalp and noticed a lot of hair loss when I would shower. At times, I would have strange sensations in my brain that I can only describe as seizure-type episodes.

Case history new patient



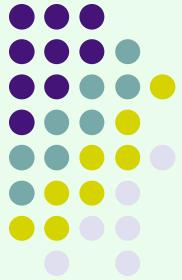
I went through years of tests and referrals from one specialist to another. Over the past 15 years, I had been tested for Lyme disease (via the ELISA) at least 7 times - all negative according to the doctors. I was told that I had clinical depression and was put on several different antidepressants, all of which made my symptoms much worse. I basically gave up and decided that I was going to have to live with my symptoms because it seemed that no one was able to help me.

In April 2002, I developed a rash all over my body. A few days later, I began getting flu-like muscle aches and a low-grade temperature. I went to my family doctor and was told that I had a spider bite and was put on prednisone. After a few days, I started getting terrible pain shooting through my shoulders and rib cage. I was then told that I had shingles and was put on an antiviral medication.



Case history new patient

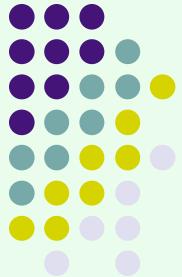
I developed a high fever and after several trips to the emergency room over the next month, I was finally diagnosed with mycoplasma pneumonia. After at least a month of bed rest, I finally started to improve from the pneumonia, but I was still very sick. The pains increased and traveled throughout my body. The nerve pain was unbearable; I still had a constant fever, was very weak and had terrible night sweats. A rash continued over most of my body. I was sent to Rheumatology, Endocrinology, Thoracic Medicine and Dermatology to no avail. I was finally referred to one of the “top doctors” in the Infectious Disease Department of (*local medical center*). When I asked him how long I should be concerned about my abnormal temperature, his exact words to me were, “Stop taking your temperature.” At that point, I lost all faith in the conventional medical society.



Treatment

- “*It is a....physician’s moral and ethical duty to treat patients appropriately. The bulk of the worldwide clinical literature, plus the experience of literally tens of thousands of Lyme patients all support the truth that Lyme and its associated co-infections are not easy to diagnose, not easy to treat, and that an individualized approach, often involving prolonged treatment courses, is needed to successfully treat the chronically ill patient.”*

Joseph J. Burrascano, Jr. MD
Lyme rally June 2, 2006
Connecticut State Assembly

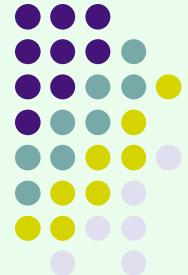


Treatment

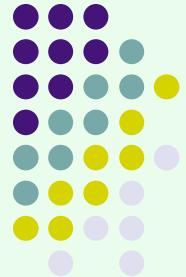
- Length of treatment is dictated by the clinical course
- Adequate treatment can reverse debilitating neurodegenerative and neuropsychiatric syndromes
The ILADS Working Group, *Expert Review of Anti-infective Therapy* 2004; 2(1) S1-S13
- Psychiatrists can be primary treating clinicians or support those that do treat
 - Psych drugs can be very helpful in controlling symptoms
 - Therapy can help the stresses of chronic illness and difficulties in finding appropriate treatment

Two Standards of Care

ILADS vs. IDSA



- International Lyme and Associated Diseases Society (ILADS)
 - The ILADS Working Group, *Expert Review of Anti-infective Therapy* 2004; 2(1) S1-S13
- Infectious Disease Society of America (IDSA)
 - Wormser, et al., *Clinical Infectious Diseases* 2006; 43(9): 1089-1134



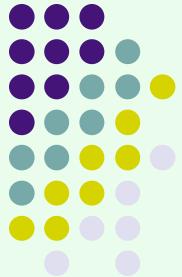
Caveats

- “Failure to recognize Lyme disease early in its course can result in the development of a chronic illness that is only temporarily or partially responsive to antibiotic therapy”

Fallon et al., The Underdiagnosis of Neuropsychiatric Lyme Disease in Children and Adults. *The Psychiatric Clinics of North America* 1998; 21(3): 693-703

- “Failure to recognize and treat the underlying infectious disease can lead to severe neuropsychiatric disability and, in some cases, death due to suicide.”

Fallon, Lyme Borreliosis: Neuropsychiatric Aspects and Neuropathology *Psychiatric Annals* 2006; 36(2): 120-128



Caveats

- In 1989, Dr. Andrew Pachner predicted that:
“If, as it now seems, the Lyme spirochete is indeed highly neurotrophic and able to remain dormant in the CNS for long periods, we may well see a sizable number of individuals who currently have latent neuroborreliosis presenting in the future with symptomatic infection.”

Pachner, A. Neurological Manifestations of Lyme Disease, the New “Great Imitator” *Reviews of Infectious Diseases*. 1989; 2(6): S1482-S14850.