Caracteristici Clinice de Boala Lyme si Scleroza Multipla

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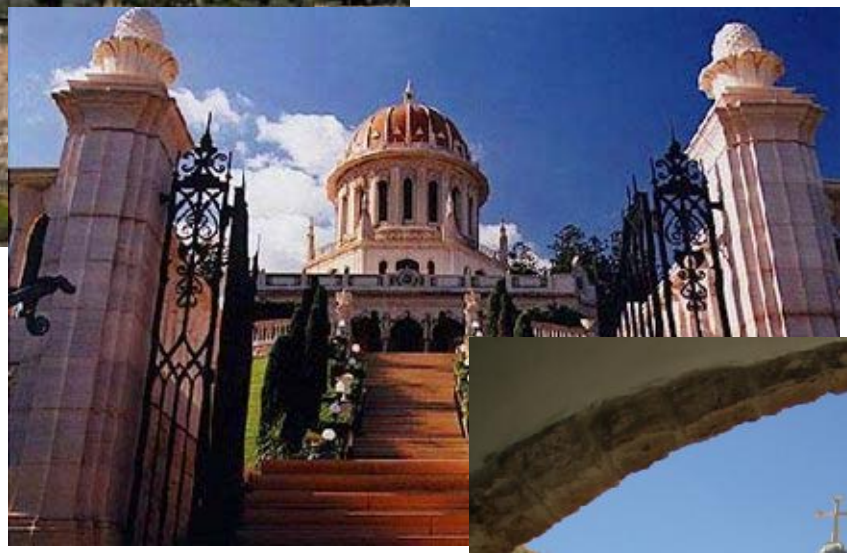

Clinical Manifestations : Lyme Disease & Multiple Sclerosis

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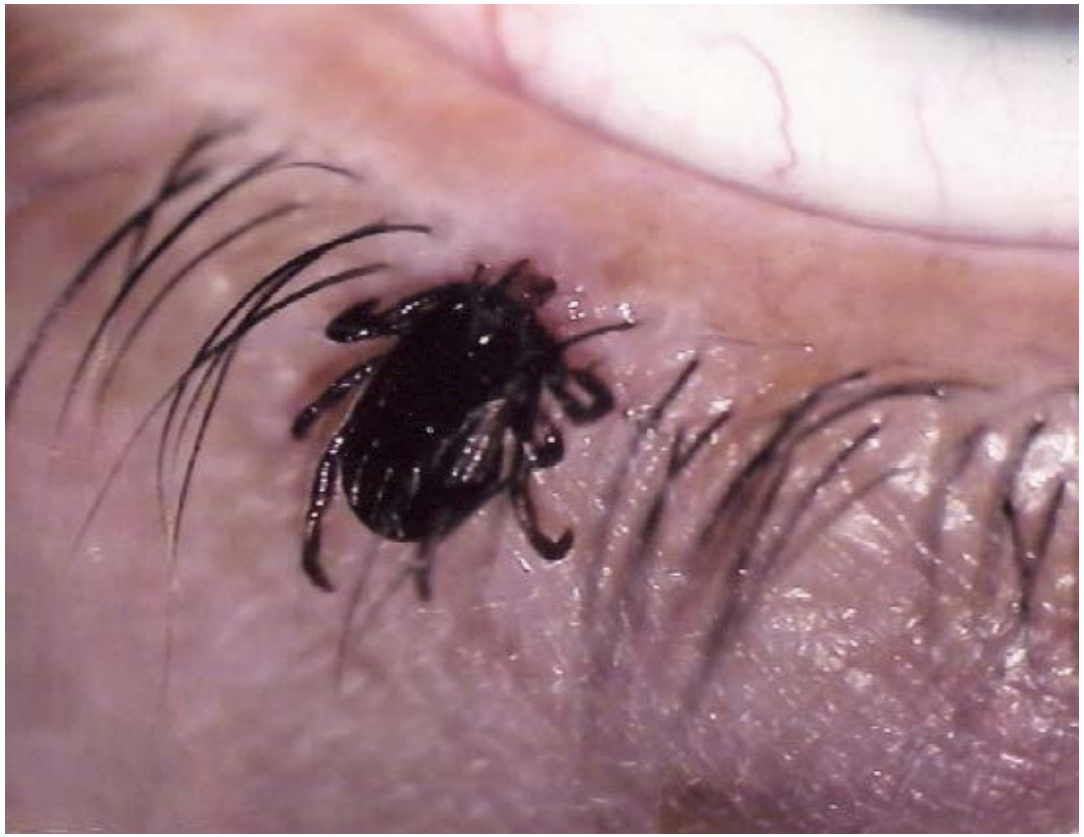
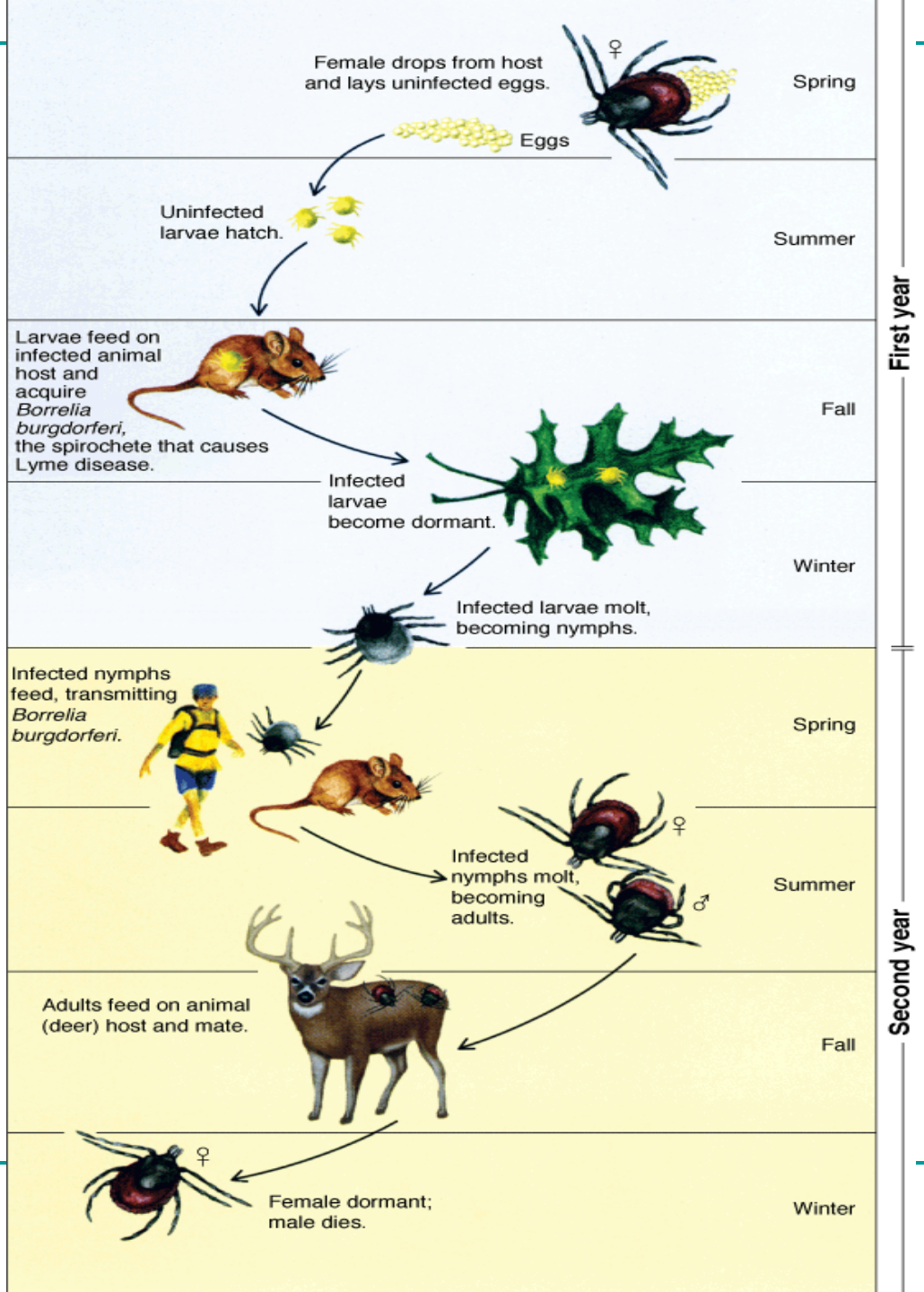
Lyme Borreliosis - Epidemiology

- Most common vector-borne disease in **USA**
- 15,000 cases of Lyme are reported yearly in USA
- 90% of cases are reported in endemic pockets in 8 states along the Atlantic coast
- Annual reported incidence may exceed 100/100,ooo
- In Europe, most prevalent in forested areas such as Scandinavia and Central Europe
- In southern Sweden, annual incidence 69/100,000
- In highly endemic areas it can reach 160/100,000



Clinical Manifestations of Lyme Disease

- Tick-borne illness caused by 3 species of gram (-) spirochete, ***Borrelia burgdorferi*** sensu lato
- B. burgdorferi undergoes enzootic cycles between ixoid ticks-***Ixodes ricinus*** (Europe), ***I.scapularis*** and ***pacificus*** (USA) – and small mammal reservoirs
- Three species are pathogenic in humans: ***B.burgdorferi*** sensu stricto (USA, Europe), ***B. garinii*** and ***B. afzelii***


Female drops from host and lays uninfected eggs.
♀
Eggs
Spring
Uninfected larvae hatch.
Summer
Larvae feed on infected animal host and acquire *Borrelia burgdorferi*, the spirochete that causes Lyme disease.
Fall
Infected larvae become dormant.
Winter
Infected larvae molt, becoming nymphs.
Infected nymphs feed, transmitting *Borrelia burgdorferi*.
Spring
Infected nymphs molt, becoming adults.
♀
♂
Summer
Adults feed on animal (deer) host and mate.
Fall
♀
Female dormant; male dies.
Winter
First year
Second year

Clinical features

- Clinical manifestations can classically be divided into 3 phases: early localized, early disseminated and late disease
- *Early localized*: erythema migrans, with or without constitutional symptoms, within 1 month after tick bite
- *Early disseminated*: multiple erythema migrans lesions, within days-weeks after infection, and/or neurologic, cardiac findings, within weeks-months after infection
- *Late Lyme*: intermittent or persistent arthritis, esp the knees, and/or rare neurologic problems (encephalopathy or polyneuropathy), within months-few years after inf.

Clinical features

- However, the disease may become manifest at any stage, stages may be skipped or may coincide
- For *daily clinical practice* it is more useful to distinguish between:

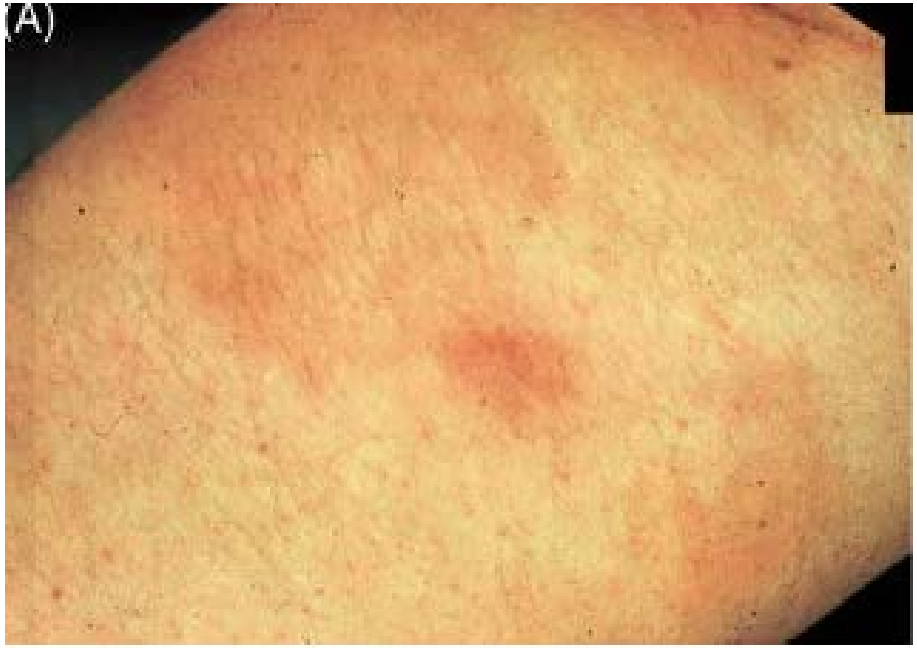
early disease or acute phase (erythema migrans, acute neuroborreliosis, carditis, early arthritis)

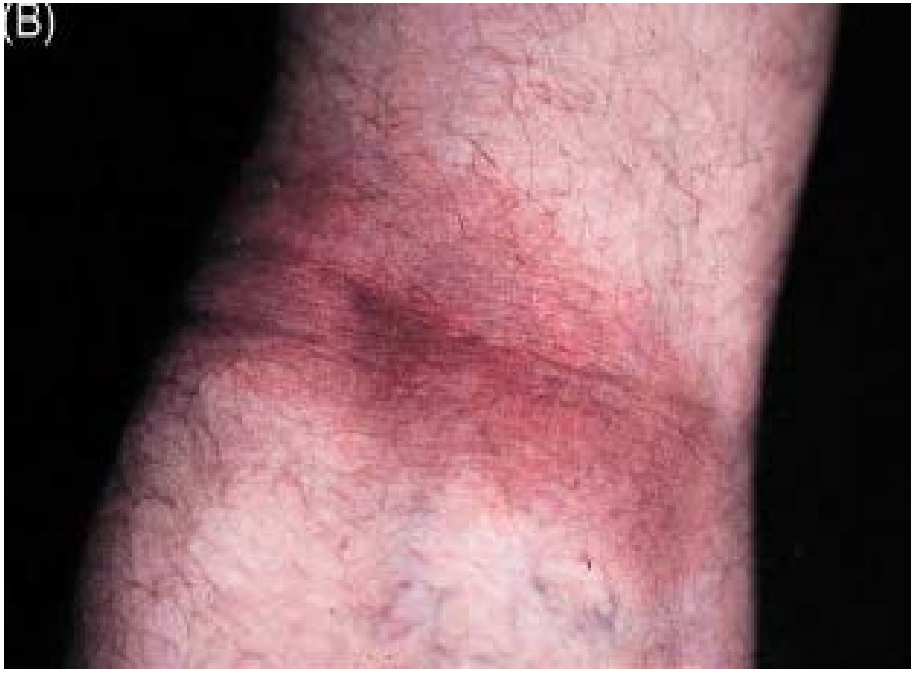
late or chronic/persistent disease (arthritis, acrodermatitis)

Dermatoborreliosis

- Erythema migrans, the pathognomonic skin lesion, can be accompanied by signs of systemic inflammation: low grade fever, chills, arthralgias, myalgias and malaise
- Headaches and paresthesias may reflect early neurological dissemination
- EM starts as a red macule or papule at the site of tick bite
- After an incubation period up to 8 wks the lesion gradually expands (“migrates”)
- The typical sites are: belt region, posterior thigh, popliteal fossa, groin, axilla or hairy area on the head

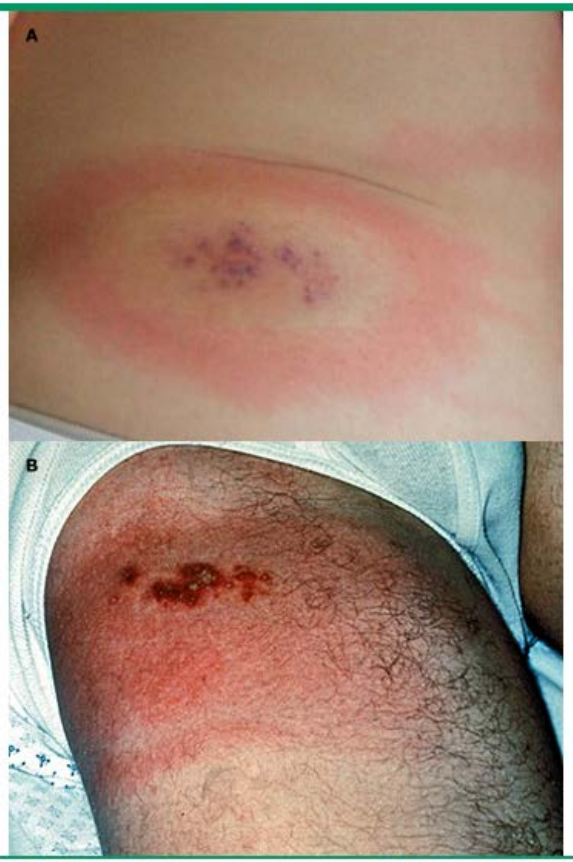
Erythema Migrans





In Europe, lesions lasting for a longer period will clear in the central part, leaving a demarcated ring and a small red spot inside, which is the initial tick bite place

Vesicular erythema migrans (EM)



Panel A) EM lesion in a patient with Lyme disease. The lesion has the complex "bull's eye" appearance with central clearing and vesicular lesions. Panel B) Vesicles may appear near the center of an erythema migrans lesion. This patient subsequently developed facial nerve palsy and had positive serology for Lyme disease.
Panel A courtesy of Robert Basow, MD; Panel B courtesy of Eugene D Shapiro, MD, FAAP.

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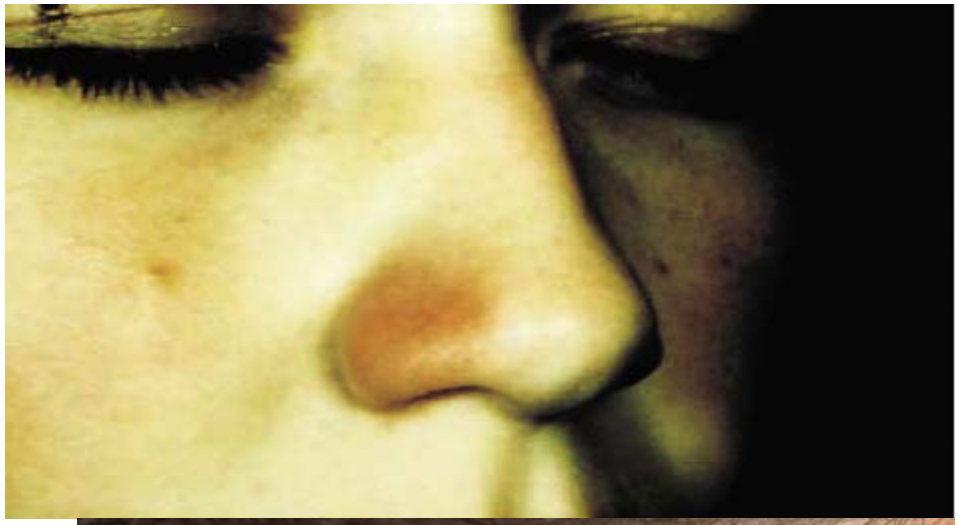
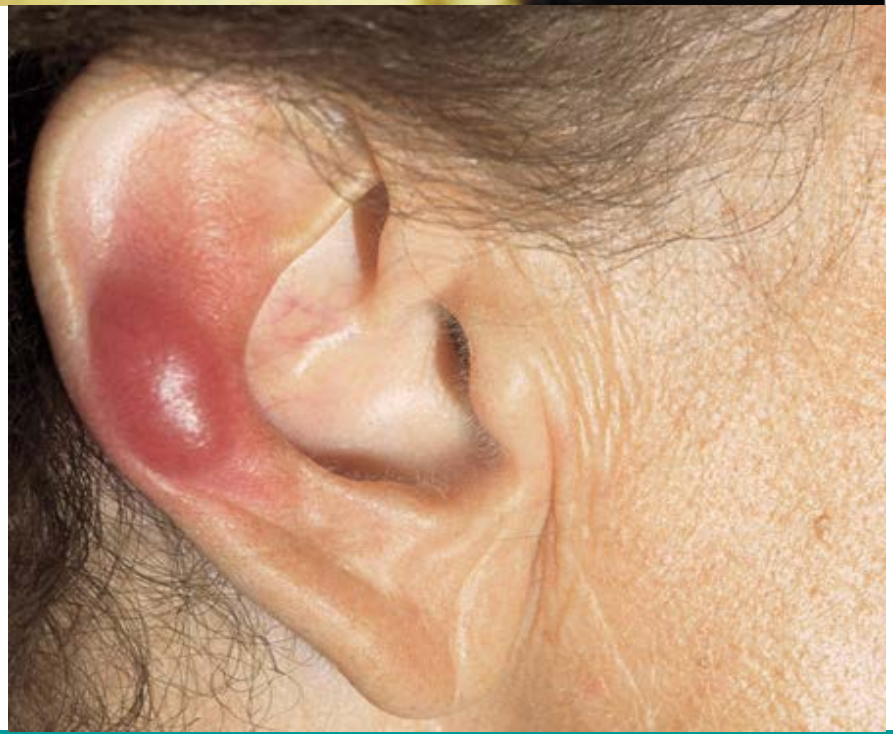
Borrelial lymphocytoma

In Europe, borrelial lymphocytoma is a rare cutaneous manifestation that occurs during the early phase of infection; it is a bluish-red swelling located on the ear lobe and the nose in children, and near the nipple and forehead in adults; pathology reveals a dense lymphocytic infiltration of the cutis and subcutis

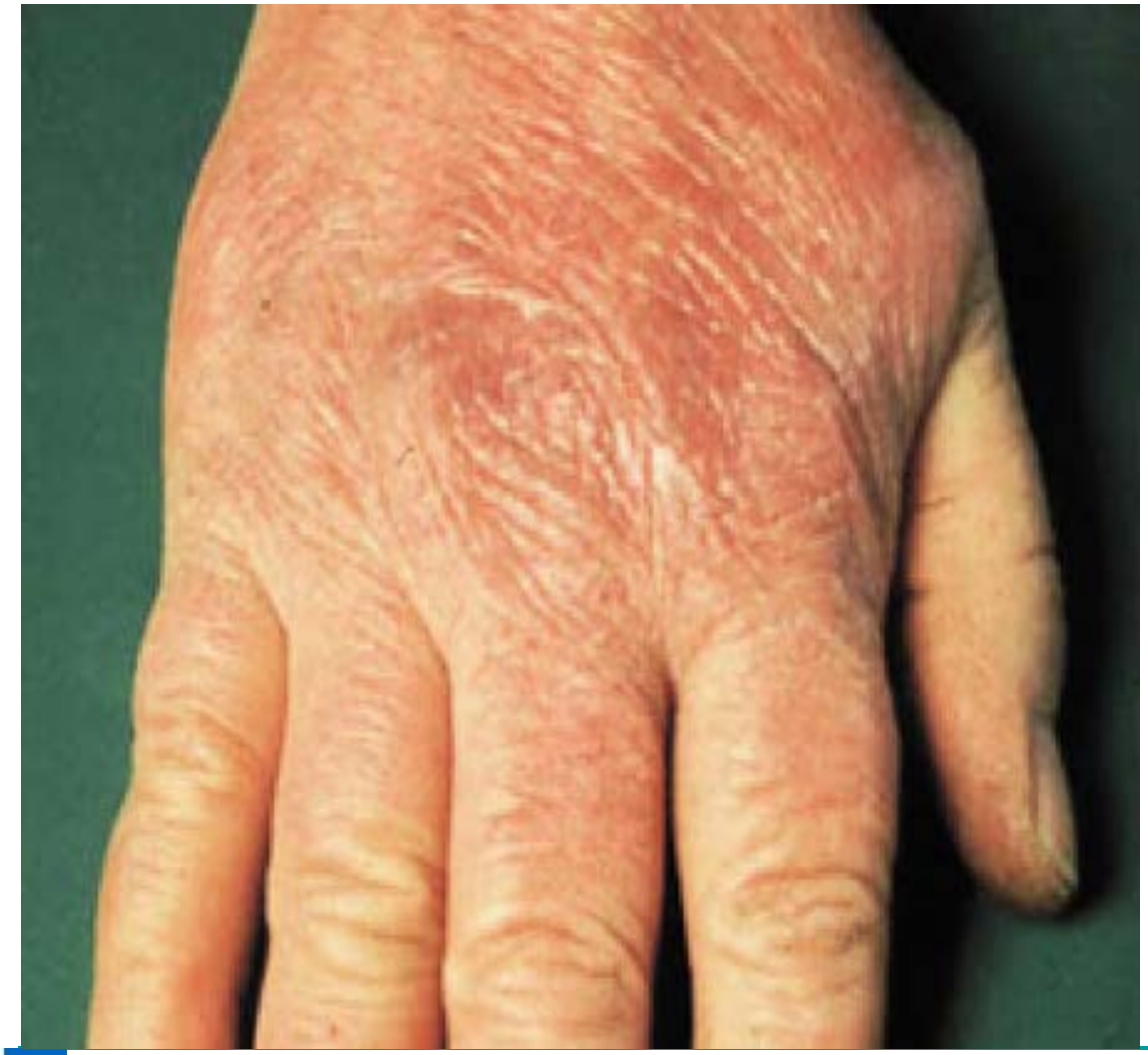


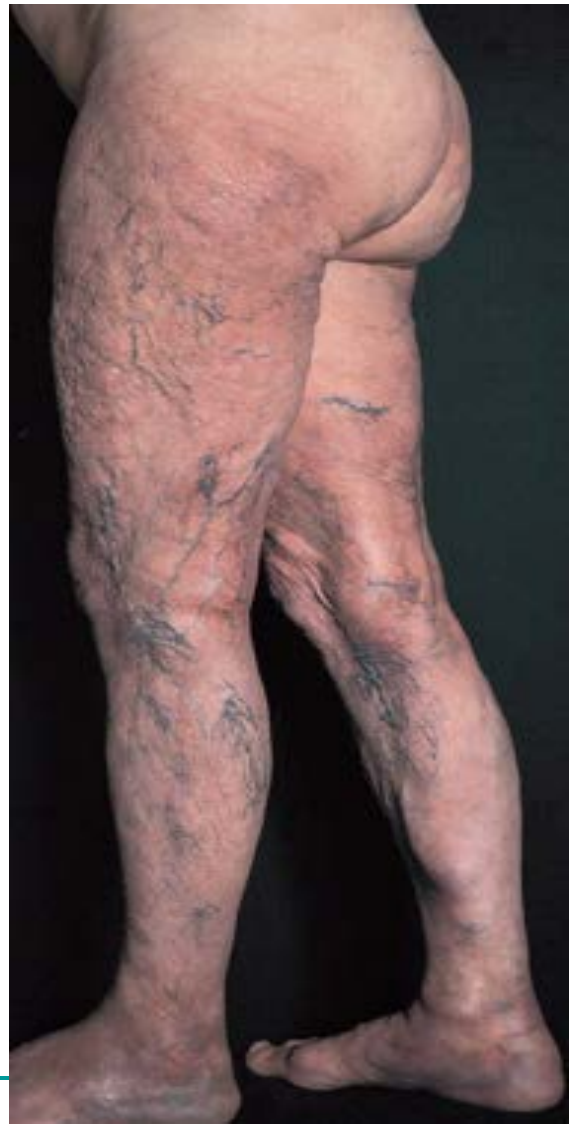


Acrodermatitis Chronica Atrophicans

- ACA is most common in untreated European women patients above 40 years of age
- It occurs more than a year after the initial infection
- It is characterized by a unilateral extended distal atrophic skin lesion preceded by inflammatory, oedematous violaceous stage
- A cigarette-paper-like appearance with a wrinkled violet thin skin without hair and translucent veins is typical
- Frequently it is associated with pain in the joints underneath the skin lesion (“arthrodermatitis”)

Acrodermatitis Chronica Atrophicans





Neurological disorders in Lyme disease

Presumed process	Peripheral nervous system	Central nervous system
Diffuse neuro-inflammatory		
		Lymphocytic meningitis
Multifocal neuro-inflammatory		
	Mononeuropathy multiplex	Myelitis (with radiculopathy)
	Cranial neuropathy (5–10%)	Encephalitis (very rare)
	Radiculopathy (?3–5%)	
	Plexopathy (lumbo-sacral, brachial)	
	Confluent mono-neuropathy multiplex	
Non-neurological inflammatory		
		Encephalopathy (common)

Neuroborreliosis

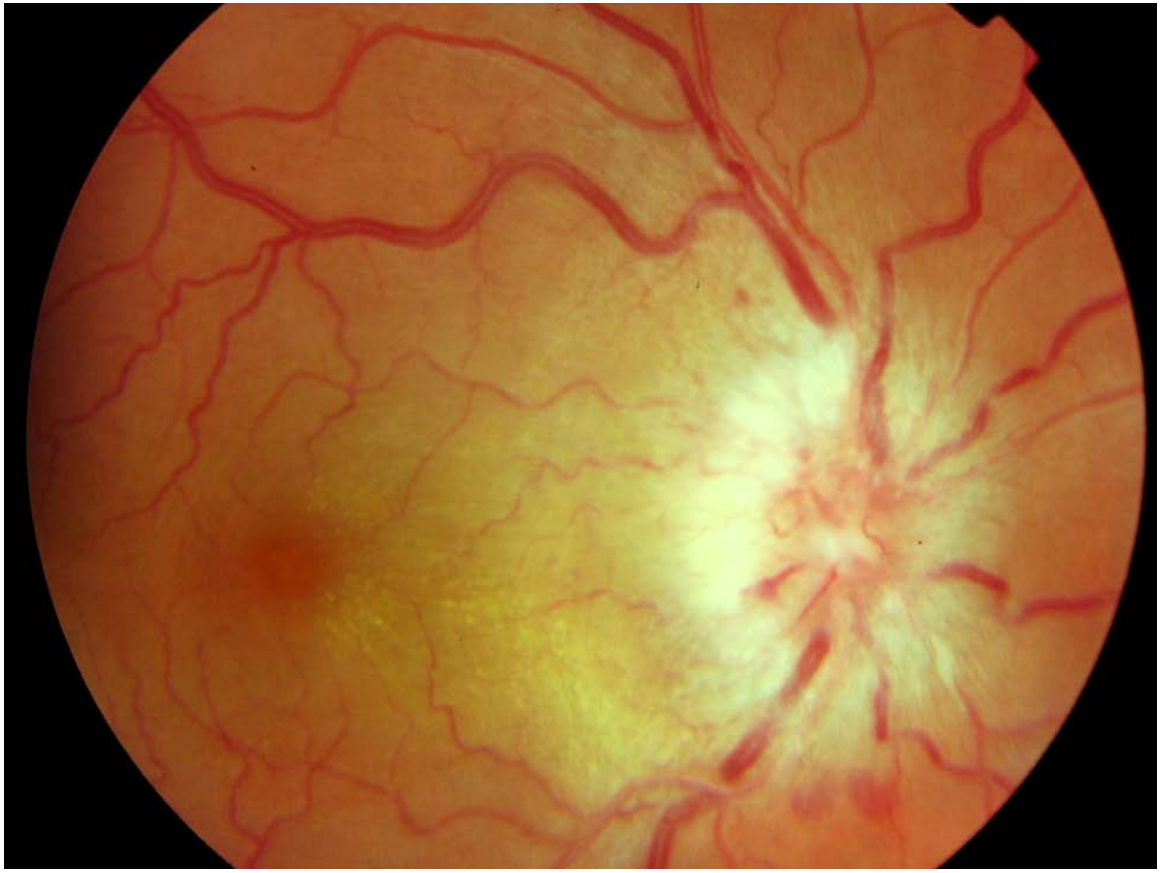
- In 15%, typical neurological symptoms develop within weeks-months after the tick bite
- Cranial neuropathy (Bell's palsy, may be bilateral mostly in children; abducens paresis; **optic neuritis**)
- Meningitis, especially in children
- Radiculoneuropathy, alone or in combination (accomp by meningitis=Bannwarth's syndrome); is a very painful, acute condition, with an increase in pain at night
- LP is necessary to establish the diagnosis
- CSF: lymphocytic pleocytosis, elevated protein, OCB, elevated immunglob/alb, PCR *B. burgdorfer*i DNA

Chronic Neurological Lyme disease

- The rare manifestations of the chronic disease, which occur months-years after infection, include:
- Distal symmetric polyneuropathy, often with acrodermatitis; mononeuritis multiplex, stroke-like disorders, caused by cerebral vasculitis; chronic encephalitis, encephalomyelitis
- Meningoencephalomyelitis characterized by slowly progr courses with increasing spastic para-, tetra- or hemiparesis
- Rare cases of demyelinating encephalopathy resemble **multiple sclerosis**

Ocular manifestations of Lyme disease

- Ocular involvement is rare, and may include: conjunctivitis, keratitis and all varities of uveitis
- Optic neuritis and perineuritis are classical manifestations of Lyme neuroborreliosis in Europe
- It has been described in association with meningoradiculitis and chronic encephalomyelitis
- Low-grade meningitis associated with IICP has a PTC-like fundoscopic presentation
- Isolated forms of ON are rare; at least 6 were described
- The picture is of uveitis-assoc neuroretinitis, with neuroretinal edema and patchy hyperfluorescence in FA



Lyme-associated papillitis with macular hard exudates

Other systemic manifestations of Lyme disease

- **Lyme carditis** is rare, occuring in 5% of patients
- Typical manifestations are: conduction abnormalities with varying degrees of AV block, BBB, AF, tachycardias
- In Europe, rare cases of chronic Lyme carditis, resulted in cardiomyopathy, even with a fatal course
- In USA, **arthritis** is the main manifestation of Lyme infection, with about 60% of untreated patients developing joint manifs, weeks-years after infection
- In most cases, there is a mono-or-oligoarticular course, predominantly affecting the knees, ankles and elbows, usually with massive effusions


HELP!

Multiple Sclerosis

- The most common chronic autoimmune inflammatory demyelinating disease of CNS
- Affects more than 1 million individuals worldwide
- Risk of developing the disease is related to genetic and environmental factors
- Typically presents between ages of 18 and 45, and affects more women than man (3:1)
- The risk of developing MS is approx 1 per 1000 (0.1%) in the general population
- This risk increases to 20-40 per 1000 (2%-4%) when a 1st degree relative is affected by MS

Multiple Sclerosis

- There is an association between latitude and MS, with the risk of MS increasing from south to north
- High frequency areas of the world, with prevalence of 60 per 100,000 or more, include all of Europe, southern Canada, northern USA, New Zealand and southeast Australia
- MS is a heterogeneous disorder with variable clinical and pathologic features, reflecting different pathways to tissue injury; but the cause is unknown
- MS begins as an inflammatory autoimmune disorder mediated by autoreactive lymphocytes

Neuropathology

- Lymphocytes are primed through Ag presentation by B cells, macrophages and microglia
- Activated lymphocytes adhere to CVS endothelium through vascular adhesion molecular interaction
- These cells release metalloproteinases, which break down BM collagen and fibronectin and allow for trafficking of inflammatory cells into CNS
- Once inside CNS, activated lymphocytes secrete cytokines (TNF, INF-G), leading to activation of B cells, complement, free radical and superoxide release
- Myelin, axon and oligodendrocytes are damaged

Classification

- MS is divided into various subtypes based on the clinical course; which are determined by distinctive pathogenic, genetic and immunologic factors
- Most (85%) pts initially have *relapsing remitting* course
- Without treatment, most of them transition to *secondary progressive* form, which has insidious neurologic decline with fewer or no clinically recognized relapses
- *Primary progressive* form occurs in 10% of pts is characterized by a steady decline from onset with predominately myelopathic symptoms
- *Progressive relapsing* form has initially a steady progression of dysfunction followed by exacerbations

Multiple Sclerosis

- MS is a clinical diagnosis
- There are no clinical findings that are unique to MS, but some are highly characteristic of the disease
- The typical patient presents as a young adult with 2 or more clinically distinct episodes of CNS dysfunction with at least partial resolution
- Presenting symptoms and signs may be either monofocal, consistent with a single lesion, or multifocal, consistent with more than one lesion

Clinical features of multiple sclerosis

Features suggestive of multiple sclerosis
Relapses and remissions
Onset between ages 15 and 50
Optic neuritis
Lhermitte's sign
Internuclear ophthalmoplegia
Fatigue
Uhthoff's phenomenon
Features not suggestive of multiple sclerosis
Steady progression
Onset before age 10 or after age 50
Cortical deficits such as aphasia, apraxia, alexia, neglect
Rigidity, sustained dystonia
Convulsions
Early dementia
Deficit developing within minutes

Presenting symptoms in multiple sclerosis

Symptom	Females, percent	Males, percent	Total, percent
Sensory in limbs	33.2	25.1	30.7
Visual loss	16.3	15.1	15.9
Motor (subacute)	8.3	10.4	8.9
Diplopia	6.0	8.5	6.8
Gait disturbance	3.2	8.3	4.8
Motor (acute)	4.4	4.2	4.3
Balance problems	2.5	4.0	2.9
Sensory in face	2.9	2.5	2.8
Lhermitte's sign (electric shock-like sensations that run down the back and/or limbs upon flexion of the neck)	1.6	2.3	1.8
Vertigo	1.8	1.5	1.7
Bladder problems	0.9	1.1	1.0
Limb ataxia	0.9	1.3	1.0
Acute transverse myelopathy	0.8	0.6	0.7
Pain	0.3	0.8	0.5
Other	2.6	2.5	2.5
Polysymptomatic onset	14.5	11.9	13.7

Data from Paty, D, Studney, D, Redekop, K, Lublin, F, Ann Neurol 1994; 36:S134 and Studyney, D, Lublin, F, Marcucci, L, et al, J Neurol Rehab 1993; 7:145.

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Diagnostic Criteria

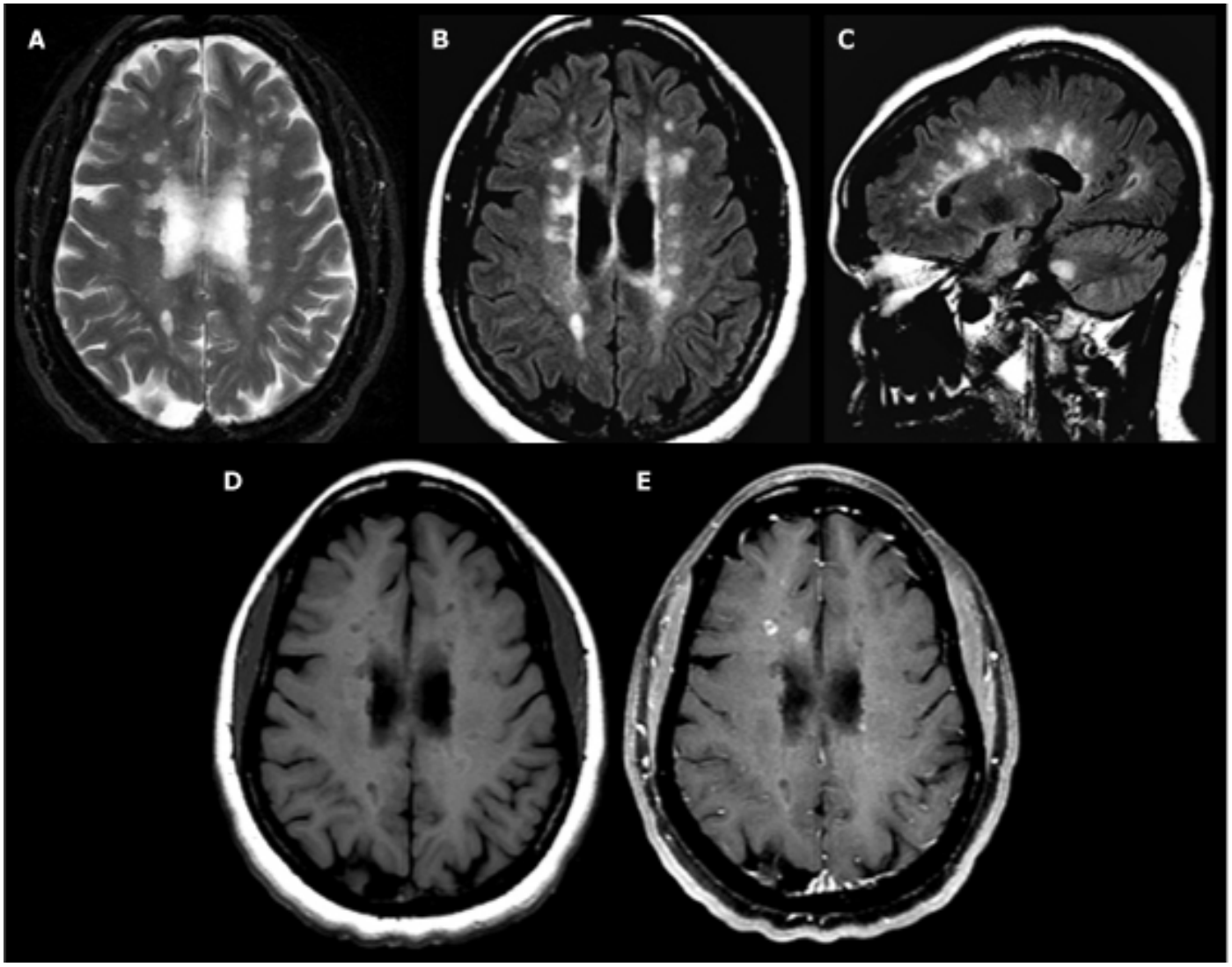
- Poser (1980); McDonald (2001, 2005, 2010)
- Core requirement of the diagnosis is objective demonstration of dissemination of CNS lesions in both space and time, based upon either clinical findings alone or a combination of clinical and MRI findings
- For pts with 1 attack who have objective clinical evidence of one lesion, the criteria require evidence of dissemination in both space and time:

1. Dissemination in space is demonstrated on MRI by one or more T2 lesions in at least 2 of four MS-typical regions of CNS (periventricular, juxtacortical, infratentorial or spinal cord)

Diagnostic Criteria

or by the development of a further clinical attack implicating a different central nervous system site

2. Dissemination in time is demonstrated on MRI by the simultaneous presence of asymptomatic Gad-enhancing and nonenhancing lesions at anytime; or a new T2 and/or Gad-enhancing lesion(s) on follow up MRI, irrespective of its timing with reference to a baseline scan, or by the development of a second clinical attack


A
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Ancillary testing in multiple sclerosis

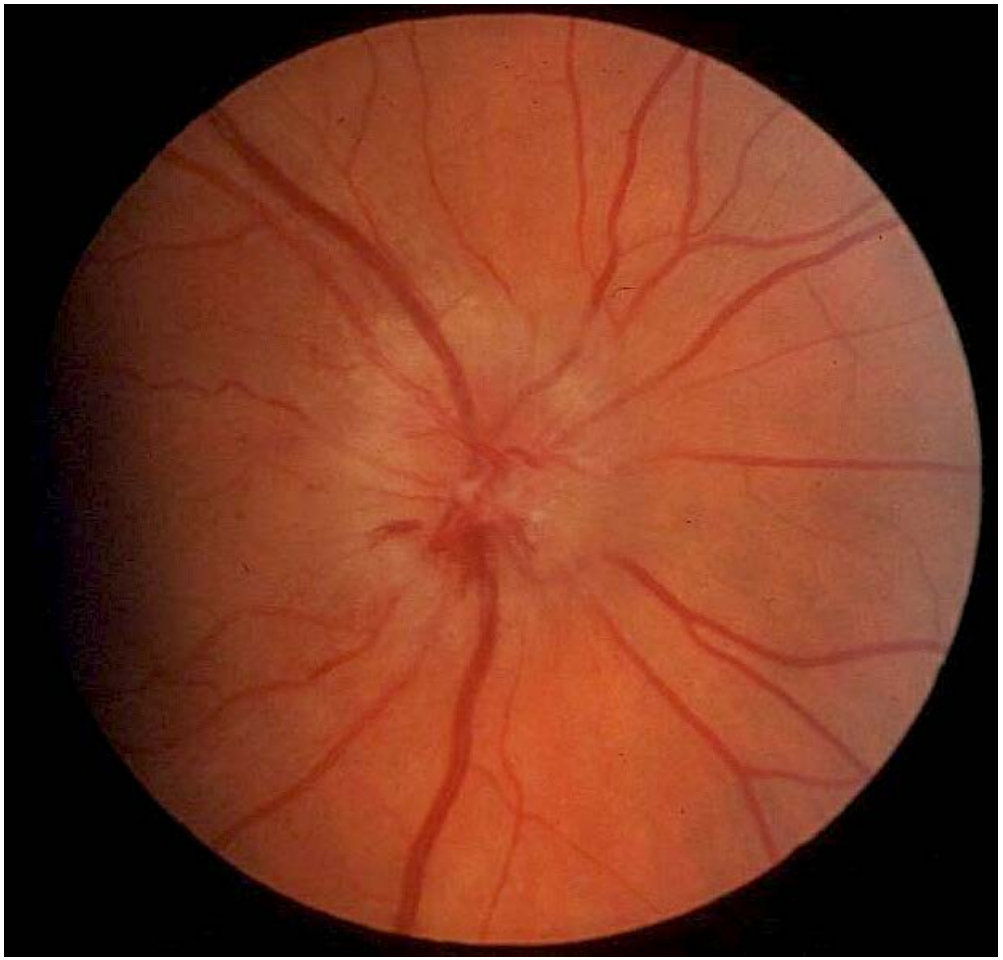
Test	Percent abnormal in patients with definite multiple sclerosis
Visual evoked response (VER)	85
Brainstem auditory evoked response (BAER)	67
Somatosensory evoked potentials (SEP)	77
Cerebrospinal fluid oligoclonal banding	85 to 95
IgG index of spinal fluid	90
Cerebrospinal fluid albumin	23
Brain MRI	70 to 95

Data from: Nuwer, MR, Packwood, JW, Myers, LW, Ellison, GW, Neurology 1987; 37:1754 and McLean, BN, Luxton, RW, Thompson, EJ, Brain 1990; 113:1269 and Rudick, RA, Whitaker, JN, in Scheinberg, P (Ed), Neurology/neurosurgery update series, Princeton, NJ, 1987 and Paty, DW, Oger, JJ, Kastrukoff, LF, et al, Neurology 1988; 38:180.

Optic Neuritis

- An inflammatory, demyelinating condition that causes acute, usually monocular, visual loss
- Is the presenting feature of MS in 15-20% of pts and occurs in 50% at some time during the course of their illness
- 2/3 of acute demyelinating optic neuritis occur in women, and develops between the ages 20-40
- The pathology is similar to acute MS plaques in the brain, with perivascular cuffing, edema MNF and myelin breakdown
- Inflammation of retinal vascular endothelium precedes demyelination, and is visibly manifest as vein sheathing

Optic Neuritis

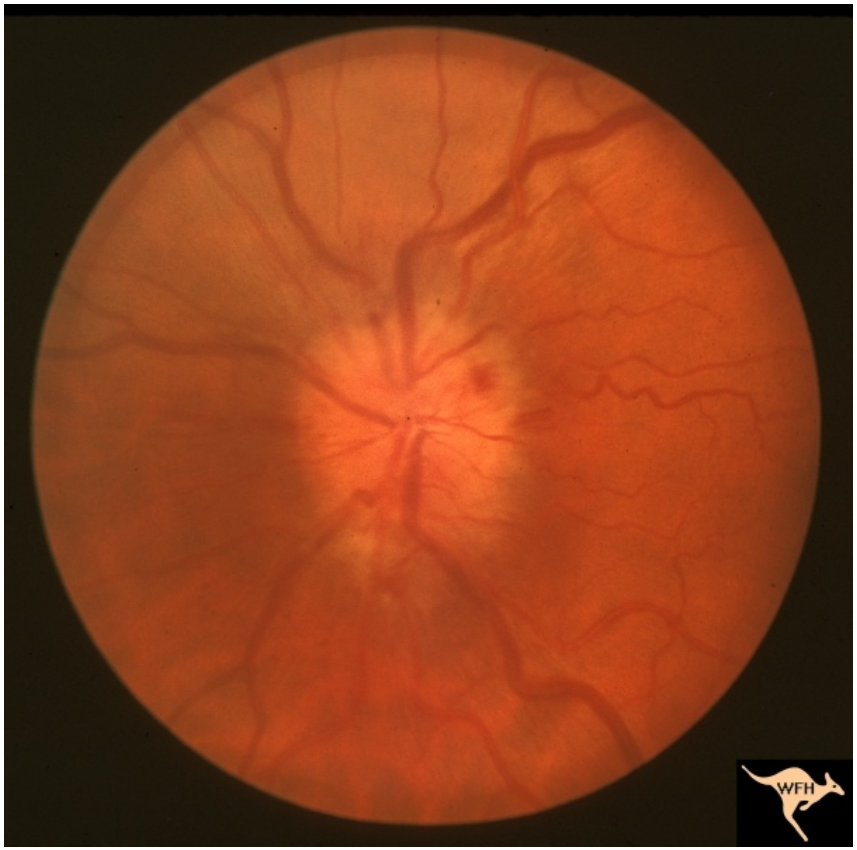


Typical Optic Neuritis Clinical Features

- Usually monocular in its presentation; 10% - in both eyes
- Vision loss develops over period of hours-days, peaking within 1-2 weeks
- In ONTT, 90+% had significant decrease in VA, 11%-6/6
- Ipsilateral eye pain-92%, often worsened with eye movement; (+) RAPD
- In ONTT, almost all types of visual field defects were seen, including *diffuse*, altitudinal, arcuate, hemianopic and cecocentral defects
- Papillitis with hyperemia and swelling of the disc, blurring of disc margins and distended veins is seen in 1/3 patients

Typical Optic Neuritis
Clinical Features-Diagnostic Tests

- Photopsias are precipitated with eye movement (30%)
- Loss of color vision is out of proportion to loss of VA
- Perivenous sheathing/periphlebitis retinae (12%), uveitis
- **Clinical diagnosis based upon the history and examination findings**
- MRI of brain and orbits (+) confirms diagnosis of acute demyelinating ON and prognostic info regarding risk of developing MS
- LP is not an essential diagnostic test, but should be considered in atypical cases
- FA isn't routinely performed, and is often normal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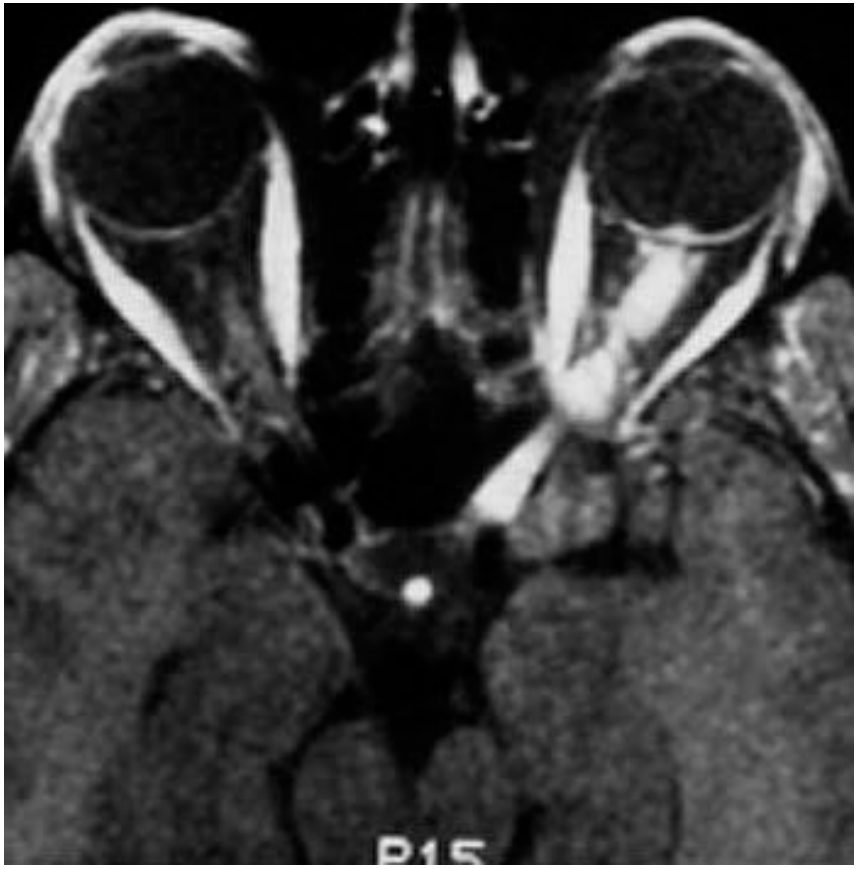
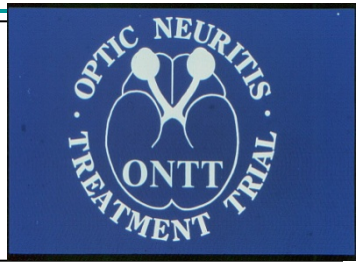


- A delay in P100 of **visual evoked response** is the electrophysiologic manifestation of slowed conduction in the optic nerve as a result of axonal demyelination
- **Optical coherence tomography** (OCT) detects thinning in most (85%) pts with optic neuritis
- Seropositivity for **aquaporin-4-specific serum autoAb** is predictive of NMO in patients with recurrent optic neuritis and negative MRI

- **ONTT protocol Optic Neuritis Treatment**

ONTT



- In the ONTT, the cumulative 5-year incidence of clinically definite MS (per Rx) was 30% following the first episode of idiopathic demyelinating ON
- The cumulative incidence increased to 40% at 12 years
- The presence of characteristic demyelinating lesions on brain MRI is a strong predictor of developing MS
- In the ONTT, the risk of MS after *10 years* was 56% among those with 1 or more lesions on MRI vs 22% among those with no lesions
- In the *15 year* follow-up, 25% of those with no lesions vs 72% of those with 1 or more lesions had developed MS

MS – Clinical Symptoms & Signs

- **INO:** abnormal horizontal ocular movements with delayed adduction and horizontal abducting nystagmus; lesion of MLF; bilaterally-coupled with vertical nystagmus on upward gaze and most suggestive of MS
- **Sensory symptoms:** numbness, tingling, pins-and-needles, tightness, coldness, swelling of limbs, radicular pains
- **Lhermitte's phenomenon:** transient sensory symptom, as an electric shock radiating down the spine or into the limbs with flexion of the neck
- **Pain:** common, dysesthetic pain, back pain, tonic spasms

MS – Clinical Symptoms & Signs

- **Vertigo:** 30-50% of patients with MS
- **Nystagmus:** 2-4% of pts with MS develop acquired pendular nystagmus later in the course of the disease
- **Motor symptoms:** paraparesis or paraplegia, spasticity
- **Coordination:** gait imbalance, difficulty in performing coordinated actions with the arms, and slurred speech may occur as a result of impairment of cerebellar pathways; intention tremor, truncal ataxia, nystagmus
- **Bowel, bladder and sexual dysfunction**
- **Uhthoff phenomenon:** small increases in body temp can temporarily worsen preexisting signs and symptoms

MS – Clinical Symptoms & Signs

- **Paroxysmal symptoms:** paroxysmal attacks of motor or sensory phenomena – diplopia, facial paresthesia, trigeminal neuralgia, ataxia, dysarthria, tonic contractions of muscles of limbs and trunk
- **Fatigue:** is a characteristic finding in MS, described as physical exhaustion, unrelated to amount of activity
- **Depression:** affective disturbance occurs in 2/3 of pts
- **Cognitive dysfunction:** 34-65% of pts have cognitive impairment per neuropsychological testing, and it may be common even at the onset of MS; the degree of cognitive decline correlates with the severity of cerebral pathology on MRI

Small clinical clues save you, small errors kill your patient!

Heuristic Points

- **Lyme disease** is a systemic infectious disease with a wide spectrum of symptoms affecting the skin, nervous system, heart and musculoskeletal system
- It is caused by 3 species of spirochaete Borrelia burgdorferi sensu lato and transmitted by Ixodes ticks
- It occurs in endemic pockets having regional variations, with an incidence from 50 to 100+ cases per 100,000
- The clinical manifestations can be divided into 2 phases: early or acute and late or chronic phase
- Lyme optic neuritis is a rare disease; its diagnosis is important since improvement of visual function is possible with specific antibiotic therapy

Heuristic Points

- **Multiple sclerosis** is the most common autoimmune inflammatory demyelinating disease of CNS, however its cause remains unknown ; MS is a clinical diagnosis
- The incidence and prevalence of MS varies geographically
- It affects more women than men, and the median age of onset is 23.5 years
- There are no clinical findings that are unique to MS, but some are highly characteristic of the disease (e.g. ON)
- Optic neuritis is an acute inflammatory demyelinating injury to the optic nerve
- In typical cases, painful, monocular visual loss evolves over several hours to several days; color vision and visual field loss and RAPD are additional characteristics

Heuristic Points

- Common symptoms of MS include sensory symptoms, motor weakness, diplopia, gait disturbance, Lhermitte's sign, vertigo, bladder problems, limb ataxia and pain
- The onset is often polysymptomatic, while the course is characterized by relapses
- MRI is the test of choice to support the clinical diagnosis of MS
- The McDonald diagnostic criteria include specific clinical and MRI findings needed for the demonstration of lesion dissemination in time and space, the core requirement of the diagnosis


Thank
You