EPIDEMIOLOGY SECTION

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LYME DISEASE - A TRIUMPH FOR SCIENCE

Since 1909, erythema chronicum migrans (ECM) has been reported in northern and middle Europe where it is associated with the bite of an ixodid tick, Ixodes ricinus, the most common tick in many parts of Europe.

The first case in the United States occurred in 1969 in a physician who had been bitten while hunting grouse in north central Wisconsin (1). In 1975, an investigation of geographic clustering of children with arthritis in Lyme, Connecticut, led to the description of a newly recognized syndrome now known as Lyme disease.

Lyme disease usually begins with the characteristic ECM skin lesion. The ECM is often accompanied by fever, malaise, headache, lymphadenopathy, stiff neck, myalgias and arthralgias. These early symptoms typically last for several weeks.

During the early phase of the disease, some patients, particularly those with the HLA-DR2 histocompatability antigen, develop an abnormal immune response which is often followed by neurologic or cardiac abnormalities or joint involvement (2).

Steere and his associates at Yale have now prospectively studied 314 patients who presented with documented ECM. Their findings regarding early signs and symptoms are summarized in Tables 1 and 2.

Table 1. Early Signs of Lyme Disease

Sign	Patients (%)
Erythema chronicum migrans*	314 (100)
Multiple annular lesions	150 (48)
Lymphadenopathy	
Regional	128 (41)
Generalized	63 (20)
Pain on neck flexion	52 (17)
Malar rash	41 (13)
Erthymatous rash	38 (12)
Conjunctivitis	35 (11)
	n = 314

equired for entry into study (2)

EPIDEMIOLOGY

Lyme disease seems to occur in three distinct foci in the United States; the Northeast, Midwest, and West. In the Northeast, the disease has been reported from southern Connecticut, southern Rhode Island, Cape Cod, southern New York and Long Island, New Jersey, Delaware and Maryland. In the Midwest, cases have been reported from Minnesota and Wisconsin and in the West, in northern California and Oregon (3). From 1975 through 1979, 512 cases of Lyme disease were recorded. Most of these were contracted within the distributional area of the deer tick, Ixodes dammini. This area extends from the southernmost tip of Delaware, northward primarily in coastal areas through Pennsylvania, New Jersey, New York, Rhode Island, and Massachusetts. This tick is also found in southern Ontario and the states of Minnesota and Michigan. In California and Oregon, the disease is associated with a different tick, I. pacificus. Disease occurrence typically begins in late May and early June and extends into the fall of the year.

ETIOLOGIC AGENT

Epidemiologic evidence suggested that Lyme disease was caused by an infectious agent transmitted by ticks of the genus Ixodes. It was not, however, until the fall of 1981 that a spirochete was detected in and isolated from adult Ixodes dammini collected on Shelter Island, New York, a known endemic area of Lyme disease (4). Convalescent-phase serum samples from patients with clinically diagnosed Lyme

Table 2. Early Symptoms of Lyme Disease (2)

Symptom	Patients (%)
Malaise, fever and lethargy	251 (80)
Headache	200 (64)
Fever and chills	185 (59)
Stiff neck	151 (48)
Arthralgias	150 (48)
Myalgias	135 (43)
Backache	81 (26)
Anorexia	73 (23)
Sore throat	53 (17)
Nausea	53 (17)
	n = 314

disease were serologically reactive to this organism by indirect immunofluorescence tests (IFA) with antibody titers ranging from 1:80 to 1:1280. In contrast, sera from persons with no history of the disease did not react with the spirochete in titers higher than 1:20. In addition, Burgdorfer and his associates demonstrated the susceptibility of the domestic white rabbit to the I. dammini spirochete.

Shortly thereafter, the same spirochete was isolated from blood, skin lesions and cerebrospinal fluid of five patients with Lyme disease (5,6). These isolates and the original one from I. dammini appeared to have the same morphologic and immunologic features. In patients, specific IgM antibody usually reached a peak between the third and sixth week after onset of symptoms while IgG specific antibody titers rose slowly and were usually highest months later when arthritis was present.

PATHOGENESIS

Histologic and microbiologic evidence support the view that the skin lesion results from an arthropod bite. Researchers believe that the spirochete is either injected into the skin or bloodstream through the saliva of the tick or deposited in fecal material on the skin. They believe that after an incubation period of 3 to 32 days, the organism migrates outward in the skin or is blood-borne to other organs or other skin sites (secondary annular lesions). It is not known whether the organism is still present when arthritis occurs (e.g., in joints) or whether it lasts only long enough to trigger a self-propagating inflammatory host response (2).

The pattern of disease occurrence in stages with remissions and exacerbations with different clinical manifestations at each stage is typical of spirochetal diseases such as leptospirosis, relapsing fever and syphilis.

VECTOR STUDIES

At present, several studies, including those by Drs. John Anderson and Lou Magnarelli of the Connecticut Agricultural Experiment Station, are in progress to clarify the natural history of this newly discovered agent. These include determining the source(s) of infecting ticks in nature, the development or behavior of the spirochete in its tick vector and the mode(s) of transmission via the tick vector.

Anderson and Magnarelli collected larval, nymphal and adult I. dammini ticks from mammals in Lyme and East Haddam. Spirochetes were observed in 35% of the motile ticks studied (7). They also surveyed wild and domestic animals collected from 1978-1982 from areas endemic for Lyme disease to determine prevalence of antibodies against different strains of spirochetes. More than 66% of 656 small and medium-sized hosts had I. dammini ticks. Parasitism ranged from 21 to 84% in these animals. Using the IFA test to detect antibodies to the spirochetes, 20% of 961 animals tested demonstrated seropositivity to the organism. Twenty-four percent of dogs tested were positive with nearly 70% having endpoints 1:1024. Samples of an additional 442 mammalian sera collected from western Connecticut where I. dammini is rare were negative(8).

DIAGNOSTIC AND TREATMENT

When ECM is present in its classical form (2) there is little else than can be confused with Lyme disease. However, in some patients the lesions may be suggestive of an uninfected tick bite, streptococcal cellulitis, erythema multiforme or tularemia. Malar rash may occur which can be confused with systemic lupus erythematosus, hepatitis B infection or erythema marginata.

The early manifestations may be confused with viral infections, especially when ECM is absent. Presenting symptoms may suggest aseptic meningitis, infectious mononucleosis, rheumatic fever or hepatitis.

Because early antibiotic therapy is beneficial, distinction from viral disease is important. Diagnostic criteria have been provided by Dr. Steere and are listed in Table 3 (4). In most cases, the diagnosis can be made from the gross appearance of ECM. In the absence of the lesion, the diagnosis should be suspected in persons living in or exposed to an endemic area who develop a flu-like or aseptic meningitis-like illness during the summer months which is accompanied by intermittent and changing symptoms.

Both oral penicillin and tetracycline have been reported to be efficacious in the treatment of Lyme disease. Patients who received penicillin or tetracycline, compared to those who received erythromycin or no therapy, had a shorter duration of ECM and associated symptoms and fewer developed subsequent arthritis. (10)

During the past three summers, Steere et al. compared the efficacy of penicillin, erythromycin and tetracycline for the treatment of early manifestations of Lyme disease and have made revised recommendations for treatment modalities based upon their experience. For adult patients early in the illness, Steere recommends "treatment with oral tetracycline, 250 mg. q.i.d. for at least 10 days and for up to 20 days if symptoms persist or recur. Phenoxy penicillin 500 mg. q.i.d. for the same duration or 2.4 million U of benzathine pencillin intramuscularly may be theoretically as effective as the tetracycline, but these treatment schedules have not yet been tested for Lyme disease. For children, phenoxymethyl penicillin is recommended, 50 mg/kg body weight/day (not less than 1 g/d or more than 2 g/d, individual doses for 10 days and up to 20 days). In cases of penicillin allergy, erythromycin, 30 mg/kg body weight/d in divided doses for 15 or 20 days is recommended. Even with these doses, relapse and major late complications may occur." (11).

Although this is not a randomized trial, it is the largest clinical study reported to date. Individuals treated with tetracycline early in the course of the disease did not develop late complications although in all treatment groups, some patients suffered from headache, residual fatigue and musculoskeletal pain following treatment. The finding that tetracycline therapy prevents the development of more incapacitating complications has important implications for clinical therapy.

FUTURE DIRECTIONS

Lyme disease is occuring with greater frequency. In 1980, about 200 cases came to the attention of the CDC; in 1982 the number recorded was more than 400 (1). This number will increase as clinicians become more aware of the clinical manifestations of the disease. Early studies suggested that the incidence of Lyme disease was 2.8 cases/1000 residents on the east side of the Connecticut River (12).

Prevalence studies from 1972-1975 provided a point prevalence rate of 4.3 cases/1000 residents in Old Lyme, Lyme and East Haddam (12).

The State of Connecticut Department of Health Services and the Centers for Disease Control are interested in establishing surveillance of Lyme disease in Connecticut. Criteria for cases and a surveillance form are being developed. It is hoped that voluntary reporting of cases will begin by March 1984.

Table 3. Lyme Disease: Current Diagnosis Criteria

A. Complete Picture

I. Onset with erythema chronicum migrans (ECM), often with one or more elements of supporting data (see IV), and subsequent characteristic (see below) involvement of nerve, heart, or joints, regardless of exposure to a known geographic area of the disease.*

ECM: A red macule or papule, usually in summer, that expands to form a large annular lesion as much as 50 cm in diameter; usually accompanied by headache, stiff neck, fever, or malaise. Subsequent multiple lesions may occur.

Nervous System: Fluctuating degress of meningoencephalitis often accompanied by cranial or peripheral neuritis, almost always in summer or early fall.

Heart: High degree of atrioventricular block, sometimes accompanied by evidence of myopericarditis, almost always in summer or early fall.

Joint: Short but recurrent attacks of migratory polyarthritis or oligoarticular arthritis.

B. Incomplete Pictures (II-IV)

II. Presence of ECM in a patient recently exposed to a known geographic area of the disease.

III. If ECM is absent, characteristic involvement of at least two of the three other systems in a patient recently exposed to a known geographic area of the disease.

IV. If ECM is absent, characteristic involvement of one of the three other systems in a patient recently exposed to a known geographic area of the disease with at least one element of the following supporting data and other disorders excluded.

Supporting data

Tick bite, I. dammini
Another family member with Lyme disease as defined in parts I, II, or III
Elevated serum IgM level or cryoglobulins containing IgM Genetic susceptibility, DR2

*A new geographic area of Lyme disease is defined by the presence of at least one individual with (a) ECM, (b) a characteristic pattern of subsequent nerve, heart, or joint involvement, and (c) no previous exposure to a known endemic area.

The First International Symposium on Lyme Disease will be held at the Yale University School of Medicine by invitation only from November 16-18, 1983. Topics will include information about the natural history, etiology, immunology, pathogenesis, epidemiology, vector, animal host, and treatment of Lyme disease. The proceedings will be published in the Yale Journal of Biology and Medicine (9).

Animal and vector studies are continuing at the Connecticut Agricultural Experiment Station and Yale University School of Medicine. Arnold Kornblatt, V.M.D. is interested in evaluating cases of Lyme disease in dogs and testing sera. He can be contacted directly at (203) 785-2453.

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	AMEBIASIS	BOTULISM	BRUCELLOSIS	ENCEPHALITIS (TOTAL)	Primary	Post	FOODBORNE OUTBREAKS	GONORRHEA	HEPATITIS A	HEPATITIS B	HEPATITIS NON A NON B	HEPATITIS UNSPECIFIED	LEGIONELLOSIS	LEPROSY	MALARIA	MEASLES	MENINGITIS (All Types)	Aseptic	Hemophilus influenzae	Meningococcal	Other	MUMPS	PERTUSSIS	PSITTACOSIS	RABIES IN ANIMALS	REYE'S SYNDROME	ROCKY MT. SPOTTED FEVER	RUBELLA	SALMONELLA	SHIGELLA	SYPHILIS	TUBERCULOSIS (TOTAL)	Pulmonary	Other	TYPHOID FEVER
Total Sept. 1983	4	0	0	7	7	0	5	898	8	30	9	1	1	0	0	0	41	32	0	5	4	2	0	0	1	0	0	0	106	17	15	17	12	5	0
Cumulative 1983	20	1	0	20	20	0	9	7094	54	267	37	12	27	1	9	8	221	99	34	46	42	16	1	1	6	0	3	0	738	155	142	113	105	28	2
Cumulative 1982	27	1	3	20	16	4	20	6469	54	327	17	32	33	1	13	6	166	50	31	42	45	18	5	1	5	1	1	3	692	797	113	93	66	27	2

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WELCOME ABOARD

We would like to take this opportunity to welcome Dr. Ellen E. Jones who joined our staff in August 1983. Dr. Jones received her M.D. from Columbia and recently completed a two year tour as an EIS officer in the Special Pathogens Branch, Center for Infectious Diseases, Centers for Disease Control in Atlanta. She is being assigned to Connecticut as a Preventive Medicine Resident for one year. At the present time, she is assigned to the Toxic Hazards Section, Preventable Diseases Division.

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