Tick bites during pregnancy.

1988 report & 1984 case

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Borrelia burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy

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Lyme borreliosis (LB) is a spirochetosis which, like syphilis, develops in three stages: erythema migrans, constitutional symptoms and/or lymphocytoma (Stage 1); carditis, early neurologic involvement and/or musculoskeletal symptoms (Stage 2); and arthritis, acrodermatitis chronica atrophicans and/or chronic encephalitis as part of Stage 3.[1-3] The causative agent of LB is *Borrelia burgdorferi*.[3]

Spirochetes have been identified morphologically in spleen, renal tubules and bone marrow in a newborn having died of cardiac abnormalities[4] and in heart, liver, adrenal gland and brain of a stillborn.[5] In addition, *B. burgdorferi* has been cultured from fetal liver.[5] The mothers of these infants did not receive antimicrobial therapy during pregnancy.

We now demonstrate *B. burgdorferi* in the brain and liver of a newborn whose mother had been treated with oral penicillin for LB during the first trimester of pregnancy.

CASE REPORT

In the course of a prospective study carried out since 1978,[6,7] we encountered a 37-year-old woman who was bitten by several ticks near Würzburg, Germany, in late July, 1984, during the second month of her first pregnancy. Two weeks later she observed an expanding itchy skin lesion on the left lower leg around one of the tick bites. An erythema migrans about 8 cm in diameter was noted when she attended the private office of one of us (KW) on August 13, 1984. According to a questionnaire there were no associated symptoms before, during and up to 2 years after the first visit. A mild form of erythema migrans disease, the European form of LB,[6,7] was diagnosed. The woman received 1 milli-IU propicillin (an oral penicillin similar in its action to phenoxymethylpenicillin) 3 times daily for a week. On August 20 the erythema migrans had disappeared. IgM and IgG antibody titers against *B. burgdorferi* were negative (<1:16) in an indirect immunofluorescence test on August 13 and October 23, 1984 (method as in Reference 8); however, reexamination of the sera when other tests were available a few years later yielded a significant rise of antibody titers against *B. burgdorferi* in the IgM enzyme-linked immunosorbent assay (ELISA) from <6.25 units/ml (normal range, up to 25 units/ml) on August 13 to 37.7 units/ml on October 23 and in the indirect hemagglutination test from 1:80 (negative) to 1:640 (positive) whereas the IgG ELISA remained negative (methods as in References 9 and 10). Follow-up revealed that the woman had delivered a normal appearing child on March 10, 1985, after an uneventful pregnancy. Delivery was aided by vacuum extraction. Twenty-three hours after birth the child suddenly developed difficulty in breathing and succumbed within half an hour. A resuscitation attempt was unsuccessful.

Postmortem examination showed a well-proportioned newborn with a weight of 3400 g and a length of 51 cm. On the right side of the scalp was a large swollen and hemorrhagic area, but there was no skull fracture. The brain showed no bleeding or rupture other than a small infratentorial hemorrhage. In the tentorium and falx cerebri, a few small hemorrhages were discovered. Microscopically there were cerebral and cerebellar edema and congestion. No significant inflammation was found in any organ including heart, liver, brain and kidney (placenta and spleen were not available). An immunohistologic examination of cerebral tissue and matrix of the brain for the common leukocyte antigen yielded negative results (courtesy of Dr. W. Permanetter, Department of Pathology, University of Munich). A small perivenous hemorrhage with minor aggregates of leukocytes was detected in the pons. The lungs showed extreme congestion, microscopic edema and a small amount of amniotic fluid without inflammatory signs. The cardiovascular system showed no malformations. The death of the newborn was probably due to a respiratory failure as a consequence of perinatal brain damage. Modified Dieterle[11] or modified Warthin-Starry[12] silver stains applied to paraffin sections of all available organs of the infant showed a few spirochetes strongly resembling *B. burgdorferi* in the brain (Fig. 1) and liver (Fig. 2). With an avidin-biotin method utilizing three chromogen substrates (diaminobenzidine and alkaline phosphatase chromogens I and III), *B. burgdorferi* was identified in rare paraffin sections of the brain when the monoclonal antibody H 5332 directed against outer surface protein of this organism (kindly supplied by Dr. A. G. Barbour, University of Texas, San Antonio; Fig. 3) was used.

On December 5, 1986, the mother had negative, indirect hemagglutination (1:160), IgG and IgM (14.7 units/ml) ELISA and indirect immunofluorescence tests (IgM and IgG type antibodies) and a negative *Treponema pallidium* hemagglutination. She delivered a second child on February 24, 1986, after an uneventful pregnancy. Serologic examination of this healthy infant at the age of 11 months yielded negative indirect hemagglutination and immunofluorescence tests (IgM and IgG type antibodies) and a negative IgM and IgG ELISA.

DISCUSSION

We have found *B. burgdorferi* in human neonatal brain and liver although the mother had been treated

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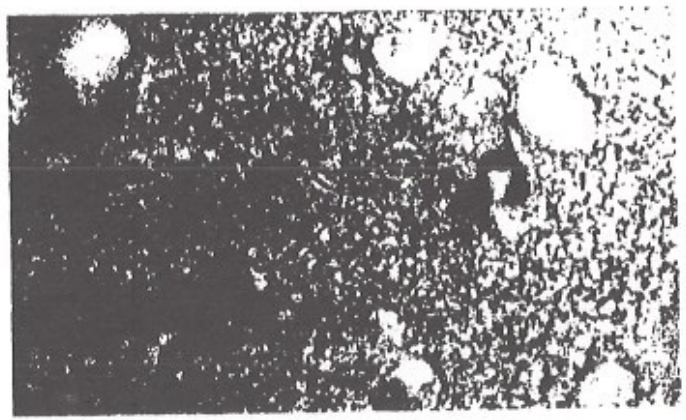

FIG. 1. Photomicrograph of brain showing a single, elongate spirochete in an extracellular position. The thickened blunt end is an effect of duplication that can be seen in cell cultures of *B. burgdorferi*. Dieterle stain, × 1250.

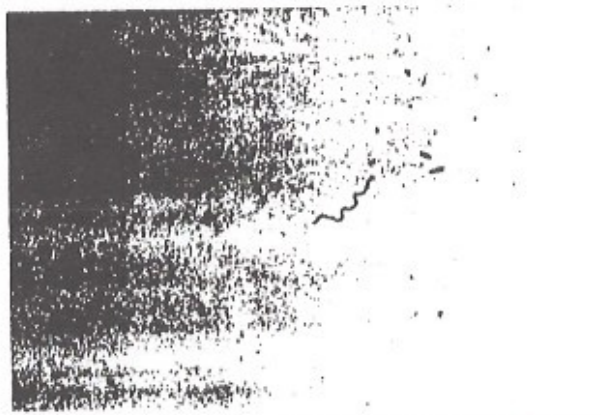

FIG. 2. This spirochete observed in the lumen of a large hepatic vein has the typical morphology of *B. burgdorferi*. Modified Warthin Starry stain, × 1300.

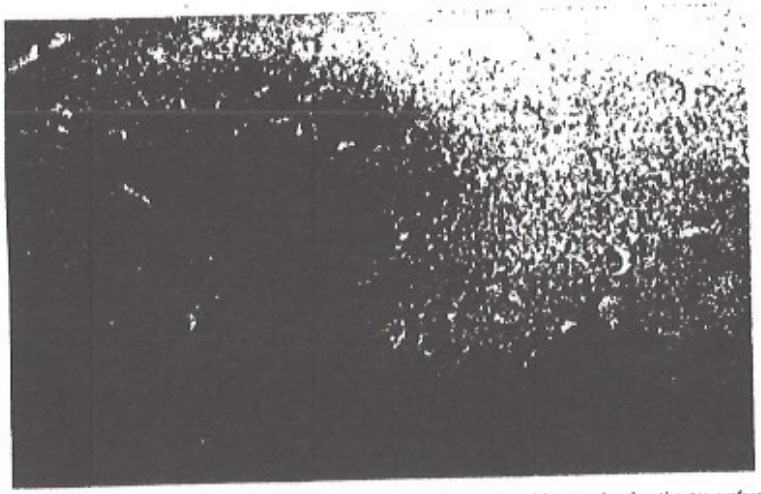

FIG. 3. *B. burgdorferi* is seen in the middle of a section of the brain. Immunostain with monoclonal anti-outer surface protein using diaminobenzidine as the chromogen and no counterstain. × 500.

with an orally administered penicillin for LB during early pregnancy.

The morphology of the spirochetes as seen by silver stain was consistent with our previous experience with *B. burgdorferi* in tissue sections.[4,5,12] Application of an immunohistochemical method allowed us to identify the spirochetes as *B. burgdorferi*.

The fact that *B. burgdorferi* can exist within human brain (Reference 5 and our case) might be important for the discussion of the pathogenesis of the recently recognized encephalitis of tertiary LB. This late type of encephalitis has thus far been based only on clinical and serologic evidence.[13,14] Interestingly, *B. burgdorferi* has recently been isolated from brain of Syrian hamsters.[15]

In our case and in two other cases of congenital LB[4,5] there was no significant inflammation in any organ examined. In erythema migrans, a hallmark of LB,[1,6,7] the presence of *B. burgdorferi* is associated with an accumulation of inflammatory cells.[12,14] However, 5 of 7 experimentally infected hamsters showed no significant inflammation in any major organ system besides lymphoid hyperplasia in the spleen, although *B. burgdorferi* could be isolated from spleen, kidney and eye of all animals.[17] The reason for the lack of inflammation remains open to speculation.

Orally administered penicillin sufficient to clear the erythema migrans of the mother was apparently not curative for our child. There have been several reports describing more severe later manifestations such as meningitis, arthritis or carditis in patients having received oral penicillin for early disease.[18,19] In the first of these reports[18] the ensuing meningitis has been treated successfully with high doses of parenteral penicillin, now the favored antibiotic treatment for neurologic involvement.[20]

We conclude that orally administered penicillin for Lyme borreliosis during pregnancy does not seem to be sufficient to prevent infection of the child. Thus we now tentatively recommend intravenous penicillin, 5 milli-IU four times daily for 10 to 14 days in pregnant women with LB. In patients allergic to penicillin, erythromycin, 500 mg four times daily, might be an alternative but experience with this regimen is limited[21] and a dosage of 250 mg four times daily has not given satisfactory results.[19]

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REFERENCES

1. Steere AC, Bartenhagen NH, Craft JE, et al: Clincal manifestations of Lyme disease. *Zentralbl Bakteriol Mikrobiol Hyg [A]* 263:201-206, 1986
2. Weber K: Die Lyme-Borreliose. *Hautarzt* 37:583-586, 1986
3. Burdorfer W, Barbour AG, Hayes SF, et al: Lyme disease: A tick-borne spirochetosis? *Science* 216:1317-1319, 1982
4. Schlesinger PA, Duray PH, Burke BA, et al: Maternal-fetal transmission of the Lyme disease spirochete, *Borrelia burgdorferi*. *Ann Intern Med* 103:67-68, 1985
5. MacDonald AB, Benach JL, Burgdorfer W: Stillbirth following maternal Lyme disease. *NY J Med* 615-616, 1987
6. Weber K, Schierz G, Wilske B, et al: European erythema migrans disease and related disorders. *Yale J Biol Med* 57:463-471, 1984
7. Weber K, Neubert U: Clinical features of early erythema migrans disease and related disorders. *Zentralbl Bakteriol Mikrobiol Hyg [A]* 263:209-228, 1986
8. Wilske B, Schierz G, Preac-Mursic V, et al: Serological diagnosis of erythema migrans disease and related disorders. *Infection* 12:331-337, 1984
9. Wilske B, Schierz G, Preac-Mursic V, et al.: IgM and IgG immune response to *Borrelia burgdorferi* in erythema migrans and neuroborreliosis. *Zentralbl Bakteriol Mikrobiol Hyg [A]*, in press, 1988
10. Wilske B, Schierz G, von Busch K, et al: Indirect haemagglutination assay (IHA) for the detection of antibodies against *Borrelia burgdorferi* (abstract). *Zentralbl Bakteriol Mikrobiol Hyg [A]*, in press, 1988
11. Duray PH, Kuanlix A, Ryan J: Demonstration of the Lyme disease spirochete *Borrelia burgdorferi* by modified Dieterle stain. *Lab Med* 16:685-687, 1985
12. Neubert U, Krampitz HE, Engl H: Microbiolocal findings in erythema (chronicum) migrans and related disorders. *Zentralbl Bakteriol Mikrobiol Hyg [A]* 263:237-252, 1986
13. Ackermann R, Gollmer E, Rehse-Küpper B: Progressive Borrelien-Enzephalomyelitis. *Dtsch Med Wochenschr* 110:1039-1042, 1985
14. Pachner AR, Steere AC: Tertiary Lyme disease: Central nervous system manifestations of longstanding infection with *B. burgdorferi*. *Zentralbl Bakteriol Mikrobiol Hyg [A]* 263:301-306, 1986
15. Johnson RC, Marek N, Kodner C: Infection of Syrian hamsters with Lyme disease spirochetes. *J Clin Microbiol* 20:1099-1101, 1984
16. Berger BW, Kaplan MH, Rothenberg IR, et al: Isolation and characterization of the Lyme disease sprochete from the skin of patients with erythema chronicum migrans. *J Am Acad Dermatol* 13:444-449, 1985
17. Duray PH, Johnson RC: The histopathology of experimentally infected hamsters with the Lyme disease spirochete, *Borrelia burgdorferi*. *Proc Soc Exp Biol Med* 181:263-269, 1986
18. Weber K: Erythema-chronicum-migrans-Meningitis: eine bakterielle Infektionskrankheit? *Münch Med Wochenschr* 116:1993-1998, 1974
19. Steere AC, Hutchinson GJ, Rahn DW, et al: Treatment of the early manifestations of Lyme disease. *Ann Intern Med* 99:22-26, 1983
20. Steere AC, Pachner AR, Malawista SE: Neurologic abnormalities of Lyme disease: Successful treatment with high-dose intravenous penicillin. *Ann Intern Med* 99:767-772, 1983
21. Weber K, Neubert U, Thurmayr R: Antibiotic therapy in early erythema migrans disease and related disorders. *Zentralbl Bakteriol Mikrobiol Hyg [A]* 263:377-388, 1986