Meningitis, cranial neuritis, and radiculoneuritis associated with *Borrelia burgdorferi* infection in a horse

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**Case Description**—A 12-year-old Thoroughbred was examined because of signs of depression, neck stiffness, and poor performance.

**Clinical Findings**—Physical examination revealed that the horse was dull, appeared depressed, was reluctant to raise its neck and head above a horizontal plane, and had a temperature of 38.5°C (101.3°F). No radiographic or scintigraphic abnormalities of the neck were found; however, high plasma fibrinogen concentration and relative lymphopenia were identified and the horse was seropositive for antibodies against *Borrelia burgdorferi*. Analysis of CSF revealed neutrophilic inflammation, and results of a PCR assay of CSF for *B burgdorferi* DNA were positive. Immunologic testing revealed severe B-cell lymphopenia and a low serum IgM concentration consistent with common variable immunodeficiency.

**Treatment and Outcome**—The horse responded well to doxycycline treatment (10 mg/kg [4.5 mg/lb], PO, q 12 h for 60 days) and returned to normal exercise. However, 60 days after treatment was discontinued, the horse again developed a stiff neck and rapidly progressive neurologic deficits, including severe ataxia and vestibular deficits. The horse’s condition deteriorated rapidly despite IV oxytetracycline treatment, and the horse was euthanatized.

**Clinical Relevance**—Nervous system infection with *B burgdorferi* should be considered in horses with evidence of meningitis and high or equivocal serum anti-*B burgdorferi* antibody titers. Evaluation of immune function is recommended in adult horses evaluated because of primary bacterial meningitis. (*J Am Vet Med Assoc* 2010;237:1180–1185)

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A 12-year-old Thoroughbred gelding was brought to the George D. Widener Hospital for Large Animals at the University of Pennsylvania for evaluation of neck stiffness and poor performance. During the several weeks prior to admission, the owner had noted that the horse seemed uncomfortable when ridden. This was particularly notable at faster speeds (ie, a canter) and when jumping. In addition, the horse’s behavior seemed to have changed; the horse appeared less active when turned out in a pasture and preferred to isolate itself from its pasture mates.

On initial physical examination, the horse’s temperature was at the upper limit of the reference range (38.5°C [101.3°F]) but heart and respiration rates were within reference limits. The horse appeared quiet and responded well to external stimuli. Body condition was thin, despite a reportedly good appetite and diet. There was mild effusion of the temporomandibular joints, and results of a PCR assay of CSF for *B burgdorferi* DNA were positive. Immunologic testing revealed severe B-cell lymphopenia and a low serum IgM concentration consistent with common variable immunodeficiency.

**Treatment and Outcome**—The horse responded well to doxycycline treatment (10 mg/kg [4.5 mg/lb], PO, q 12 h for 60 days) and returned to normal exercise. However, 60 days after treatment was discontinued, the horse again developed a stiff neck and rapidly progressive neurologic deficits, including severe ataxia and vestibular deficits. The horse’s condition deteriorated rapidly despite IV oxytetracycline treatment, and the horse was euthanatized.

**Clinical Relevance**—Nervous system infection with *B burgdorferi* should be considered in horses with evidence of meningitis and high or equivocal serum anti-*B burgdorferi* antibody titers. Evaluation of immune function is recommended in adult horses evaluated because of primary bacterial meningitis. (*J Am Vet Med Assoc* 2010;237:1180–1185)

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**Abbreviations**

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<tr>
<td>IRU</td>
<td>Increased radiopharmaceutical uptake</td>
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<tr>
<td>NCC</td>
<td>Nucleated cell count</td>
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of the vertebral column were seen. Total WBC count was within reference limits (total WBC count, 10.24 × 10^3 cells/µL; reference range, 4.3 × 10^3 cells/µL to 14.8 × 10^3 cells/µL), but a relative lymphopenia (1,428 cells/µL; reference range, 1,700 to 3,800 cells/µL) was detected. Serum fibrinogen concentration was slightly elevated (763 mg/dL; reference range, 150 to 375 mg/dL), but results of the serum biochemical analysis were otherwise unremarkable.

A nuclear scintigraphic evaluation was performed to further evaluate the neck stiffness and the lameness. This revealed moderate IRU in the region of the distal tarsal joints in the left and right hind limbs, mild to moderate IRU associated with the spinous processes of thoracic vertebrae 13 to 15, and mild IRU associated with the medial aspect of the distal phalanx of the right forelimb. Mild to moderate IRU was noted in the proximal aspect of the first phalanx in both forelimbs. No IRU was noted in the cervical portion of the vertebral column or the head.

During the first 12 hours of hospitalization, the horse’s rectal temperature remained at the upper end of the reference range (38.4°C to 38.6°C [101.2°F to 101.4°F]) and the horse remained quiet and had signs of depression. Serum samples were submitted for anti-*Borrelia burgdorferi* antibody titer testing. Testing of the sample collected at the time of admission yielded equivocal results on both ELISA (296 KELA units; positive result, > 380 units; equivocal result, 130 to 380 units; negative result, < 130 units) and western blot analysis. A subsequent sample obtained 3 days after admission yielded an equivocal ELISA result (349 KELA units). However, western blot analysis of this second sample revealed a low to moderate amount of antibody, consistent with *B burgdorferi* infection (ie, a positive result).

A sample of CSF was obtained from the lumbosacral space with the horse sedated. Laboratory analysis of the CSF revealed slight xanthochromia with an NCC of 69 cells/µL (reference range, 0 to 3 cells/µL), total protein concentration of 173 mg/dL (reference range, 47 to 69 mg/dL), and RBC count of 100 cells/µL (reference range, 0 to 167 cells/µL). Cytoplasmic analysis revealed 82% neutrophils; 12% small mononuclear cells; 6% large mononuclear cells with foamy, vacuolated cytoplasm; and a few RBCs. Findings were indicative of neutrophilic inflammation. No bacteria were seen during the cytologic examination. Bacterial and fungal cultures of the CSF did not yield any growth. Results of a western blot analysis of the CSF for evidence of *Sarcocystis neurona* infection were negative. Results of a PCR assay (OspA primer) of the CSF for *B burgdorferi* DNA were positive.

Because of the relative rarity of meningitis in mature adult horses, immunologic testing of the horse was undertaken to evaluate lymphocyte phenotype and serum immunoglobulin concentrations. Periph- eral blood lymphocyte phenotyping (Table 1) revealed CD4+ lymphocytosis and severe B-cell lymphopenia. The CD4+/CD8+ ratio was high. Serum IgG and IgA concentrations were within reference ranges (IgG, 1,200 mg/dL; reference range, 984 to 1,685 mg/dL; IgA, 210 mg/dL; reference range, 67 to 239 mg/dL), but serum IgM concentration was low (23 mg/dL; reference range, 90 to 150 mg/dL).

Treatment with doxycycline (10 mg/kg [4.5 mg/lb], PO, q 12 h for 60 days) and phenylbutazone (2.2 mg/kg [1 mg/lb], PO, q 12 h for 7 days, then 2.2 mg/kg, PO, q 24 h for 7 days) was initiated. Within the first week of treatment, the horse’s behavior and attitude were reported to improve with a return to normal head carriage and gradual weight gain. Plasma fibrinogen concentration 14 days after initiation of treatment had decreased to 440 mg/dL. The horse was then returned to its normal turnout routine.

Sixty days after treatment with doxycycline was discontinued, the horse was readmitted to the hospital because of an acute recurrence of neurologic signs. It had been noted to have a slightly stiff neck for 4 to 5 days prior to admission and shied away when approached from the left side, had difficulty turning to the left, and had a reduced appetite for grain. Treatment with phenylbutazone PO and oxytetracycline IV had been initiated by the referring veterinarian, and the horse’s condition had appeared relatively stable until the day of admission, when it acutely and rapidly deteriorated. The horse had become ataxic, developed tremors, was unwilling to walk, and leaned to the left side.

On admission, the horse had obvious left-sided vestibular deficits and was leaning heavily on the left

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**Table 1—Peripheral blood lymphocyte phenotype analysis of a horse with meningitis and a subsequent diagnosis of neuroborreliosis.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient (% positive cells)</th>
<th>Reference range (% positive cells)</th>
<th>Patient lymphocytes (1,428 cells/µL)</th>
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<tbody>
<tr>
<td>Negative control</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CD2+ T cells</td>
<td>96.5</td>
<td>87.1 ± 3.3 (all T cells)</td>
<td>100 cells/µL</td>
</tr>
<tr>
<td>CD3+ T cells</td>
<td>97.8</td>
<td>90.9 ± 2.6 (all T cells)</td>
<td>1,108 cells/µL</td>
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<tr>
<td>CD4+ T cells</td>
<td>77.6</td>
<td>64.8 ± 5.9 (CD4 T cells)</td>
<td>243 cells/µL</td>
</tr>
<tr>
<td>CD5+ T cells</td>
<td>97.8</td>
<td>92.0 ± 3.4 (all T cells)</td>
<td></td>
</tr>
<tr>
<td>CD8+ T cells</td>
<td>17.0</td>
<td>18.2 ± 3.3 (CD8 T cells)</td>
<td></td>
</tr>
<tr>
<td>B cells (CD19-like)</td>
<td>1.7</td>
<td>10.2 ± 2.5 (B cells)</td>
<td>24 cells/µL</td>
</tr>
<tr>
<td>B cells (CD21)</td>
<td>1.0</td>
<td>10.7 ± 5.2 (B cells)</td>
<td></td>
</tr>
<tr>
<td>B cells (IgM)</td>
<td>0.4</td>
<td>11.7 ± 2.1 (B cells)</td>
<td></td>
</tr>
<tr>
<td>MHC class I</td>
<td>99.8</td>
<td>99.9 ± 0.1 (B and T cells)</td>
<td></td>
</tr>
<tr>
<td>MHC class II</td>
<td>97.8</td>
<td>94.1 ± 5.1 (B and T cells)</td>
<td></td>
</tr>
<tr>
<td>LFA-1</td>
<td>99.7</td>
<td>99.8 ± 0.1 (B and T cells)</td>
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MHC = Major histocompatibility complex.
Within these segments was focal cervical neuritis with mild multifocal Wallerian degeneration. Microorganisms were not detected on Gram, Gomori methenamine silver, Zielh-Neelsen (acid-fast), or Warthin-Starry stains. Perls’ iron stain revealed numerous large macrophages that contained phagocytized erythrocytes and hemosiderin. Congo red stains were negative for amyloid deposits. Results of routine fluorescent antibody testing of the cerebral cortex and cerebellum, including the medulla, by the Pennsylvania Department of Health for rabies virus were negative. Results of a PCR assay of brain tissue and cell culture virus isolation for West Nile virus were negative. Shavings of formalin-fixed, paraffin-embedded postmortem tissues from inflamed regions of the brain were submitted for *B. burgdorferi* PCR testing. Postmortem *B. burgdorferi* PCR tests were negative. However, because of the prior diagnosis of borreliosis and the pattern, type, and distribution of the histologic lesions, a presumptive diagnosis of leptomeningitis and peripheral radiculoneuritis secondary to borreliosis was made.

![Figure 1](image1.png)

**Figure 1**—Photomicrograph of a section of cerebrum from a horse with a presumptive diagnosis of neuroborreliosis. Mononuclear inflammatory cells infiltrate the leptomeninges of the Virchow-Robbins space (arrow); small perivascular cuffs are also present (arrowhead). H&E stain; bar = 200 µm.

![Figure 2](image2.png)

**Figure 2**—Photomicrograph of a different section of cerebrum from the horse in Figure 1. Numerous lymphocytes and macrophages with rare neutrophils surround and often infiltrate blood vessels (arrow); blood vessels often have thickened, hyalinized walls (arrowheads). H&E stain; bar = 100 µm.
Discussion

The definitive diagnosis of borreliosis in horses remains challenging. It has been reported\(^6\) that 13% to 24% of horses in areas in which the disease is endemic have serologic evidence of exposure to *B burgdorferi*. Infection rate varies by season, and horses may have no definitive clinical signs. Currently, the CDC\(^7\) recommends a 2-tiered approach to the serologic diagnosis of Lyme disease in people, consisting of use of an ELISA or immunofluorescence assay as a screening test, followed by western blot analysis in patients with positive or equivocal ELISA or immunofluorescence assay results. This approach has also been adopted in the veterinary community. However, whereas the specificity of this diagnostic approach is high, the sensitivity is relatively poor (50% to 75%),\(^8\) which necessitates testing of paired samples to avoid false-negative results, as was the case for the horse described in the present report.

The sensitivity of PCR analysis of tissue samples for *B burgdorferi* has been found to be higher than that of tissue culture techniques in a study\(^9\) evaluating experimental induction of chronic borreliosis in dogs. Definitive postmortem diagnosis of persistent *B burgdorferi* infection by use of PCR analysis was unsuccessful in the horse described in the present report. However, an experimental study\(^10\) suggested that the number of *B burgdorferi* spirochetes in brain tissues is typically low in nonhuman primates infected with *B burgdorferi*. This is supported by similar findings in a human patient with neuroborreliosis, where *B burgdorferi* DNA was detected in only 1 of 6 brain tissue samples submitted for PCR analysis.\(^11\) Formalin fixation can also affect the sensitivity of PCR assays. Because only formalin-fixed paraffin-embedded specimens were available for PCR analysis for the patient in the present report, it is unclear whether results were falsely negative.

The antemortem diagnosis of neuroborreliosis in human patients is often difficult. Traditionally, demonstration of intrathecal anti-*B burgdorferi* antibody production provides the strongest evidence of infection. Because of the potential for antibody leakage across the blood-brain barrier with CNS infection, comparison of antibody titers in the CNS and serum (CNS:serum index) is required to accurately estimate intrathecal antibody production.\(^12\) However, this technique was not used in the horse described in the present report. Newer techniques, such as the use of a PCR assay for detection of *B burgdorferi* DNA, have also become more widely used for diagnosis, particularly because of the low sensitivity of culture techniques for isolation of *B burgdorferi* from the CSF.\(^11\)

Previous reports have documented arthritis and panuveitis,\(^13\) lameness,\(^14\) and encephalitis\(^15\) in horses with *B burgdorferi* infection. Localization of *B burgdorferi* to the nervous system has been described in human patients\(^16\) and reproduced in nonhuman primates.\(^17\) Signs of neuroborreliosis in human patients include encephalomyelitis, lymphocytic meningitis, radiculo-neuropathy, and cranial neuropathies, most commonly facial nerve paralysis.\(^12\) Histologic lesions include meningeal hyperemia and focal subdural hemorrhage, multifocal cerebral vasculitis, perivasculitis, leptomeningitis, and focal white matter degeneration.\(^11,18\) Vasculitis may cause changes in perfusion, which can result in white matter degeneration and progressive demyelination.\(^19\) A recent study\(^19\) involving rhesus macaques with intrathecal exposure to *B burgdorferi* identified induction of proinflammatory cytokines, chemokines, and proapoptotic genes by glial cells (mainly astrocytes and microglia) and endothelial cells. It has been proposed that these neuroimmune modulators and apoptotic regulators may contribute to the pleocellular leptomeningitis, vasculitis, and perivasculitis associated with borreliosis and may also induce neuronal and oligodendrocyte apoptosis that could result in de-myelination and progressive neurologic deterioration.\(^19\) Localization of spirochetes to the spinal roots (motor and sensory), dura mater, leptomeninges, and dorsal root ganglia has been noted in immunosuppressed nonhuman primates experimentally infected with *B burgdorferi*.\(^17\) Dose-dependent adherence of *B burgdorferi* has been noted in primary rat brain cultures\(^20\) and C6 glioma cell lines; particular affinity for the extracellular matrix was noted. *Borrelia burgdorferi* can express an
assortment of adhesins to facilitate dissemination and adhesion after transmission to the host; these include proteins to bind to integrins, fibronectin, decorin, and nondecorin glycosaminoglycans. Decorin binding has been found to confer protection to B. burgdorferi from host humoral immunity in experimentally infected mice. The ability to adhere to host tissues and evade host humoral immunity may explain chronic B. burgdorferi infection. However, additional studies are required to confirm whether this can occur in horses. Immunosuppression has been found to be of importance in the experimental induction of clinical borreliosis in adult dogs and the increased spirochete tissue load in studies involving nonhuman primates. In the horse described in the present report, concurrent common variable immunodeficiency was strongly suspected on the basis of the immunologic testing performed. However, additional testing to confirm the diagnosis of common variable immunodeficiency (ie, in vivo vaccine response) had not been performed at the time the horse’s condition suddenly deteriorated. It appears highly likely that common variable immunodeficiency played a role in the development of meningitis, radiculoneuropathy, and vasculitis secondary to borreliosis in this horse. However, it is uncertain whether neuroborreliosis can develop in immunocompetent horses and this warrants further investigation.

Optimal antimicrobial treatment for horses with high anti–B. burgdorferi antibody titers and evidence of clinical disease remains unclear. Some experimentally infected ponies treated with doxycycline PO orcefotiam continued to have positive results for tissue culture for B. burgdorferi after 28 days of treatment. However, treatment with tetracycline IV resulted in negative postmortem tissue culture results. Because of poor penetration of the blood-brain barrier, oxytetracycline was not given initially to the patient described in the present report, and a clinical response was noted following treatment with doxycycline PO despite reports of negligible CSF concentrations following administration of doxycycline PO in clinically normal horses. However, the subsequent recrudescence of clinical signs in this patient was consistent with a report of failure to consistently eliminate B. burgdorferi from the tissues of experimentally infected ponies following treatment with doxycycline. It is unclear whether therapeutic doxycycline concentrations can be achieved in the CNS of patients with altered blood-brain barrier permeability or whether the clinical improvement reported was associated with the reported anti-inflammatory properties of doxycycline. In vitro testing of B. burgdorferi isolates with amoxicillin, tilmicosin, and enrofloxacin showed susceptibility to tilmicosin. However, SC tilmicosin injection in horses produces severe inflammatory reactions at the injection site and it is contraindicated for use in horses in the commonly available preparation. Further investigation into the most appropriate antimicrobial treatment for the treatment of borreliosis in horses is still required. Appropriate antimicrobial treatment in human patients with borreliosis remains equally controversial. Several studies have failed to show a benefit of prolonged antimicrobial treatment, particularly in patients with chronic infection. Published guidelines for human patients recommend treatment with amoxicillin or doxycycline (or alternatively cefuroxime) PO in early infections and parenteral administration of ceftriaxone (alternatives include cefotaxime and penicillin G) in patients with acute neurologic or cardiac involvement.

a. Animal Health Diagnostic Laboratory, College of Veterinary Medicine, Cornell University, Ithaca, NY.

References

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**From this month’s AJVR**

**Determination of the prevalence and severity of metacarpophalangeal joint osteoarthritis in Thoroughbred racehorses via quantitative macroscopic evaluation**

Richelle H. Neundorf et al

**Objective**—To determine the prevalence and severity of osteoarthritis in the metacarpophalangeal joints of Thoroughbred racehorses via development and validation of a quantitative macroscopic evaluation system.

**Sample Population**—Metacarpophalangeal joints from 50 Thoroughbred racehorses.

**Procedures**—Joints were collected from horses that died or were euthanized within 60 days of racing. Metacarpophalangeal joints were assessed for osteoarthritic degeneration by use of macroscopic and histologic scoring systems, polarized light microscopy, and cartilage biochemical analysis. The global macroscopic score for the entire metacarpophalangeal joint was based on factors that reflected the size and severity of lesions as well as the involvement of weight-bearing surfaces.

**Results**—One-third of all 2- and 3-year-old horses had partial- or full-thickness cartilage lesions and osteoarthritis. Osteoarthritis severity increased until age 6 in this population. Significant correlations were found between macroscopic grade and age, cause of death, glycosaminoglycan depletion, and loss of superficial cartilage zone polarized light intensity.

**Conclusions and Clinical Relevance**—The macroscopic system devised for this study had good correlations with quantitative methods. Two- and 3-year-old horses had full-thickness cartilage lesions that may have been career limiting. Year-to-year attrition and a small population of older horses may have led to underestimation of the prevalence of osteoarthritis in older horses. The macroscopic scoring system was reliable when used by nonexpert and expert users. (*Am J Vet Res* 2010;71:1284–1293)