CASE REPORT

Tick-borne encephalitis virus as a possible cause of optic neuritis in a dog

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Abstract

A 3-year-old spayed female Siberian Husky was presented due to acute vision loss. Examination revealed bilateral optic neuritis and lymphocytic meningoencephalitis. The serum (1:800) and cerebrospinal fluid (CSF; 1:200) immunoglobulin (Ig)G titers for tick-borne encephalitis virus (TBEV) were elevated as were the serum IgG titer for *Anaplasma phagocytophilum* (1:640) and serum IgM titer for *Toxoplasma gondii* (1:20). Intracytoplasmic inclusion bodies such as ehrlichial or anaplasmal morulae were not observed in the CSF or blood smear. The dog was treated with methylprednisolone and doxycycline. The left eye regained vision; the right eye remained blind. Anti-inflammatory therapy was stopped on day 18 after diagnosis. Four days later the dog showed evidence of hyperesthesia in the cervical region. Analysis of CSF showed no abnormalities and CSF IgG titers for TBEV and *A. phagocytophilum* were negative. Funduscopic evidence of active papillitis was absent on day 22 in the left eye and on day 86 in the right eye. On day 243, the dog was presented again with lethargy, ataxia, disorientation and temporary head tilt. The IgG titer for TBEV was again elevated in the CSF (1:800) and in serum (1:400). After interpretation of all findings, we assume that meningoencephalitis and optic neuritis in this patient was caused by TBEV and associated immune-mediated inflammation. In endemic areas, TBEV should be considered as cause of optic neuritis in dogs.

Key Words: dog, optic neuritis, papillitis, tick-borne encephalitis virus

CASE REPORT

History

A 3-year-old spayed female Siberian Husky was presented to the Clinic for Surgery and Ophthalmology of the University of Veterinary Medicine in Vienna, Austria for acute loss of vision. The owner reported a 2-week history of reduced vision in the dog’s right eye, a serous discharge from both eyes and abnormal hind limb gait. The dog was vaccinated against canine distemper virus, canine adenovirus, *Leptospira* spp., rabies virus and canine parvovirus. The dog was living in a tick-borne encephalitis virus (TBEV)-endemic area in Austria and had been infested with several ticks in the previous 2 months.

Initial clinical findings

Upon presentation (day 0), the dog appeared depressed, had normal body temperature (38.4 °C), and mild hyperesthesia of the lumbar region. Ophthalmic examination revealed dilated pupils with complete loss of menace response, dazzle reflexes, and pupillary light reflexes (PLRs) in both eyes (OU). No abnormalities of the anterior segment were detected. The optic nerve head of the right eye (OD) was mildly swollen, and mild peripapillary edema and some hemorrhages were present (Fig. 1a). The optic nerve head of the left eye (OS) was more notably swollen and elevated (10 diopters) with a peripapillary retinal detachment and some peripapillary hemorrhages (Fig. 1b). The optic disc margins were indistinct in both eyes. The clinical diagnosis was optic neuritis OU.

Differential considerations

Potential causes of optic neuritis in the dog include infectious agents (canine distemper virus, *Toxoplasma gondii*, *Ehrlichia canis*, *Rickettsia rickettsii*, systemic mycoses, granulomatous meningoencephalitis, undefined meningoencephalitis,
trauma,\textsuperscript{11} toxins,\textsuperscript{12} idiopathic optic neuritis,\textsuperscript{4,5} orbital inflammatory lesions,\textsuperscript{5} and optic nerve or orbital neoplasia.\textsuperscript{5} In children, infection with \textit{Borrelia burgdorferi} has caused optic neuritis.\textsuperscript{12}

\textbf{Laboratory tests}

Results of the hemogram and serum chemistry profile were within normal limits. The serum immunoglobulin (Ig)G titers for TBEV and \textit{Anaplasma phagocytophilum} were elevated (Table 1). The serum IgG titer for \textit{T. gondii} was negative, whereas the IgM titer was of questionable significance (Table 1). Serum antibodies to \textit{E. canis}, \textit{B. burgdorferi} or \textit{Neospora caninum} were not detected.

Cerebrospinal fluid (CSF) pressure was measured using an arterial blood pressure transducer device (Hewlett Packard, Anesthesia Monitoring System, Viridia, MA, USA) and was mildly elevated (176 mm H\textsubscript{2}O; reference range: < 170 mm H\textsubscript{2}O). Analysis of the CSF showed 144 nucleated cells/\mu L (reference range: < 5), elevated protein (30 mg/dL; reference range: < 30 mg/dL) and glucose (100 mg/dL; reference range: 40–70 mg/dL) concentrations, and 5–10 erythrocytes/\mu L (ref. range: < 30/\mu L). The nucleated cells present in the CSF comprised 85% small lymphocytes, 10% monocytes and 5% granulocytes. Intracytoplasmic inclusion bodies such as ehrlichial or anaplasmal morulae were not observed in the CSF or blood smear. The CSF IgG titer for TBEV was 1:200 (Table 1). Neither IgM nor IgG specific for canine distemper virus could be detected in the CSF.

\textbf{Diagnosis}

Bilateral optic neuritis and lymphocytic meningoencephalitis, most likely secondary to infection with TBEV, were diagnosed.

\textbf{Treatment}

In patients with optic neuritis associated with meningitis or meningoencephalitis, anti-inflammatory therapy with corticosteroids should be started immediately to decrease the inflammatory response and therefore protect or minimize

\textbf{Figure 1.} Fundus photographs on day 0. (a) OD: The optic disc is swollen with mild peripapillary edema. (b) OS: The optic disc is markedly swollen and elevated. The peripapillary retina is detached. Note some peripapillary hemorrhages.

\textbf{Table 1.} Serum and CSF antibody titers for various infectious agents

<table>
<thead>
<tr>
<th>Sample type</th>
<th>Antibody type</th>
<th>TBEV\textsuperscript{*}</th>
<th>\textit{A. phagocytophilum}\textsuperscript{†}</th>
<th>\textit{T. gondii}\textsuperscript{‡}</th>
<th>Canine distemper virus\textsuperscript{†}</th>
<th>\textit{B. burgdorferi}\textsuperscript{†}</th>
<th>\textit{E. canis}\textsuperscript{†}</th>
<th>\textit{N. caninum}\textsuperscript{†}</th>
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<tbody>
<tr>
<td></td>
<td>Serum IgG</td>
<td>CSF IgG</td>
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<td>Cut-off</td>
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<td>1:100</td>
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<td>1:80</td>
<td>1:20</td>
<td>1:40</td>
<td>1:20</td>
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<tr>
<td>Day 0</td>
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<td>1:200</td>
<td>1:640</td>
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<td>1:20</td>
<td>Negative</td>
<td>1:64</td>
<td>1:64</td>
</tr>
<tr>
<td>Day 22</td>
<td>1:400</td>
<td>Negative</td>
<td>1:160</td>
<td>Negative</td>
<td>ND</td>
<td>ND</td>
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<td>Day 213</td>
<td>Negative</td>
<td>ND</td>
<td>1:80</td>
<td>Negative</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Day 243</td>
<td>1:400</td>
<td>1:800</td>
<td>1:80</td>
<td>Negative</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND, not done; TBEV, tick-borne encephalitis virus.

* Enzyme-linked immunoassay.

† Immunofluorescence.

‡ Agglutination.
damage to the optic nerve. On day 0, a single dose of prednisone (10 mg/kg; Solu-Dacortin®, Merck, Vienna, Austria) was administered intravenously. Because infectious causes had not been ruled out at this stage, a single dose of trimethoprim-sulfonamide (15 mg/kg; Borgal®, Hoechst Roussel Vet, Vienna, Austria) also was administered subcutaneously.

**Follow-up**
The following day (day 1), vision still appeared to be absent OU. Both pupils were widely dilated. The menace response and direct and consensual PLRs were absent OU. Dazzle reflex was present OS, but absent OD. Peripapillary edema OS was markedly reduced. No changes in funduscopic findings could be detected OD. Prednisone (5 mg/kg) was administered intravenously once daily for 2 days. Then, beginning on day 3, methylprednisone (2 mg/kg every 24 h; Urbason®, Aventis Pharma, Vienna, Austria) was administered orally. Based upon the serum IgG titer for *A. phagocytophilum*, antibiotic therapy was changed to doxycycline (10 mg/kg orally every 12 h; Vibramycin®, Pfizer Corporation, Vienna, Austria) and continued for 3 weeks.

On day 5, the pupils were still dilated and direct and consensual PLRs were negative. The dazzle reflex and menace response were present OS, but absent OD. There was no change in funduscopic findings OD (Fig. 2a). The optic disc OS was only slightly elevated and swollen and the peripapillary edema had almost resolved (Fig. 2b). Signs of lumbar hyperesthesia and depression were no longer detected.

On day 12, the optic discs OU were less swollen than on day 5, but their borders were still indistinct (Fig. 3a,b). The

**Figure 2.** Fundus photographs on day 5. (a) OD: No changes are noted since day 0. (b) OS: The optic disc is swollen and slightly elevated. The peripapillary edema has nearly resolved relative to day 0.

**Figure 3.** Fundus photographs on day 12. (a) OD and (b) OS: The optic discs are less swollen than day 5 but still have indistinct borders.
PLRs, menace response and dazzle reflex were unchanged relative to day 5. Methylprednisone dose was reduced to 1 mg/kg every 24 h for 3 days, then 0.5 mg/kg every 24 h for 3 days, and stopped on day 18. Four days following cessation of anti-inflammatory therapy (day 22), the dog exhibited hyperesthesia in the cervical region. The left eye was still sighted and had a menace response and dazzle reflex. The right eye remained apparently blind. In both eyes the pupils were dilated and PLRs were negative. The right optic nerve head was elevated slightly with indistinct borders (Fig. 4a); however, the optic disc OS appeared normal (Fig. 4b). Analysis of CSF on day 22 showed no abnormalities. The CSF antibody titers for TBEV, A. phagocytophilum and B. burgdorferi were negative (Table 1). The serum IgG titer for TBEV and for A. phagocytophilum had decreased (Table 1). Therapy with methylprednisone (1 mg/kg orally every 24 h) was initiated again.

On day 31, cervical hyperesthesia was no longer observed. To reduce the amount of methylprednisone administered at that time (0.5 mg/kg orally every 24 h), azathioprine (Imurek®, Aventis Pharma, Glaxo Wellcome Pharma, Vienna, Austria) was administered orally (0.5 mg/kg every 24 h for 1 week and then 0.5 mg/kg every 48 h).

The owners chose to discontinue all therapy after just 6 days (day 37). On day 46, the dog was presented to a veterinary internist who noted blindness, lethargy, and hyperesthesia of the head and neck regions. No ophthalmic examination was performed at this visit. Methylprednisone (1 mg/kg orally every 24 h for 7 days, then 0.5 mg/kg orally every 24 h for 7 days, then 0.3 mg/kg orally every 24 h) and doxycycline

**Figure 4.** Fundus photographs on day 22. (a) OD: No changes are noted since day 12. (b) OS: No further funduscopic evidence of optic neuritis or peripapillary chorioretinitis is noted.

**Figure 5.** Fundus photographs on day 86. The right (a) and left (b) optic discs appear normal.
Infection with CSF sample and slightly elevated protein (56 mg/dL). or immune-mediated meningoencephalitis, other infectious agents that could cause meningoencephalitis were also investigated because they could not be ruled out based on CSF analysis alone. The high IgG titer for TBEV in serum and CSF supports a diagnosis of tick-borne encephalitis (TBE). Austria is an endemic area for TBEV and the dog was infested with several ticks in the 2 months preceding the first episode of visual impairment. Recurrent TBE has not been described previously; however, this dog apparently had a recurrent TBEV infection within 1 year of initial infection, suggesting the initial immune response was inadequate.

TBEV is an arbovirus belonging to the family Flaviviridae, genus Flavivirus. In central Europe, the vector for this virus is the tick *Ixodes ricinus*, which limits the infectious period due to its seasonal activity. Mammals and birds are natural hosts but demonstrate varying susceptibility. In humans living in endemic areas in Europe, TBEV is a frequent cause of meningitis, meningoencephalitis, meningoencephalomyelitis and meningoencephalomyelitis and meningoencephalomyelitis and meningoencephalomyelitis and meningoencephalomyelitis. Dogs appear more resistant than humans to infection with TBEV. Only a few publications report clinical cases of TBE in dogs. After an estimated incubation period of 5–9 days, fever, lethargy and diverse neurologic signs may occur. Four different clinical outcomes have been described following infection of dogs with TBEV: seroconversion without clinical disease, or peracute, acute or chronic disease syndromes. In the majority of cases, dogs seroconvert without clinical evidence of TBE. The IgG seroprevalence for TBEV in dogs in Austria is 24%. Immunosuppression is probably a prerequisite for the development of clinical signs. Because the immune response in this dog did not protect him from development of clinical disease or from apparent reinfection, an immune deficiency is possible.

In the peracute course, dogs die within 3–7 days due to progressive, multifocal neurologic signs. Typically, TBE manifests itself as multifocal central neurological system disease with involvement of forebrain, brainstem, cerebellum, meninges or spinal cord. In early stages of the disease, serum and CSF antibody titers cannot be detected in most cases and histopathologic examination is required for diagnosis. Characteristic neuropathological findings are severe meningoencephalomyelitis with necrosis of neurons and glial cells, neuronophagia, glial nodules, perivascular cuffs and diffuse infiltration of leptomeninges. The lesions are most prominent in the brainstem and cerebellum. Viral antigen could be found using a polyclonal antibody in only a few of these cases. This is presumably due to a similarly rapid clearance mechanism to that which occurs in other forms of flaviviral encephalitis.

In the acute course of TBE, clinical signs improve and often resolve completely after 1–3 weeks. A more chronic course in which neurologic signs improve after 1–6 months also has been reported. Because antiviral therapy does not exist, only supportive and anti-inflammatory therapies are possible.

Optic neuritis has not been described previously in canine TBE. Apart from severe optic neuritis, this dog had only

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very mild signs of meningoencephalitis. Because therapy was not started until 2 weeks after clinical signs were first observed, the inflammatory response had likely caused irreversible damage to the right optic nerve. Initiation of anti-inflammatory therapy within a few hours of total vision loss likely reduced damage to the left optic nerve. The left eye retained vision but PLRs were absent. The most likely explanation for these clinical findings is a lesion of the afferent arm posterior to the lateral geniculate body or of the efferent arm of the PLRs because iris atrophy or synchia were excluded as reasons for the absent PLRs.

During the second episode of meningoencephalitis (beginning on day 243), the dog exhibited more severe neurologic signs. However, the optic nerve heads appeared ophthalmoscopically normal. Mild perineural contrast enhancement of the right optic nerve noted on MRI at that time indicated either altered vascular permeability or increased blood circulation in this area. Other signs consistent with acute optic neuritis such as increased nerve diameter and signal enhancement without contrast in other sequences were not seen. These MRI changes were therefore considered to be more supportive of chronic inflammation.

After termination of anti-inflammatory therapy, the dog showed hyperesthesia in the cervical region. The CSF was normal at that time so meningitis did not seem to be the cause of hyperesthesia. Extrameningeal tissue damage is a possible explanation for transient hyperesthesia.

In acute TBEV infection, one would typically expect a four-fold rise in serum antibody titer over a 2-week period. However, TBEV antibody titer development varies greatly in clinical reports. Of 17 dogs, only 7 showed a one- to three-fold increase in serum antibody titer, whereas titer decreased in 8 dogs and remained stable in 2 (interval between first and second sample: 2–6 weeks). In a case report describing chronic TBEV infection in two dogs, serum antibody titer decreased after 3 weeks. In this disease, variability in antibody titer development might represent rapid clearance of this virus and differing immune status of infected dogs. In our patient, antibody titer for TBEV in CSF was higher than in serum (Table 1), suggesting that intrathecal antibody production occurred.

The high serum IgG titer for *A. phagocytophilum* suggests that this dog had also come into contact with this organism, which is also transmitted by *I. ricinus*. Apart from the high antibody titer and meningitis, no other evidence suggestive of anaplasmosis such as thrombocytopenia, anemia, bleeding tendency, polyarthritis, weight loss, tender abdomen, anterior uveitis or chorioretinitis was seen in our patient. Moreover, the cells noted in the initial CSF sample were not typical of anaplasmosis, and intracytoplasmic anaplasma morulae were not detected in neutrophils or monocytes from blood or CSF. In the only case report of granulocytic ehrlichiosis (GCE) associated with meningitis in a dog, typical signs of GCE were present and CSF analysis showed pleocytosis with 48% neutrophils and 52% large mononuclear cells. The positive serum IgM and IgG titers for *T. gondii* in our patient on days 0 and 213, respectively, suggest that this dog probably had contact with this protozoon. In humans, characteristic clinical findings in patients with ocular toxoplasmosis include focal retinochoroiditis or a retinocchoroidal scar with adjacent moderate to severe vitreous inflammation. Anterior optic neuritis is an unusual manifestation of toxoplasmosis in humans and is often associated with vitreous inflammation and formation of peripapillary white inflammatory lesions or granulomas.

The authors are aware of only one report of optic nerve involvement in a dog with toxoplasmosis. In that case, chorioretinitis, iridocyclitis and diffuse gliosis of the optic nerve with pseudocyst formation were noted. *Toxoplasma* organisms were also identified in the retina. In our patient, no signs of uveal or retinal inflammation were observed. When taken in combination with the very low serum antibody titer and negative CSF titer for *T. gondii*-specific antibodies, toxoplasmosis was unlikely to be the cause of optic neuritis in our patient.

In central Europe, systemic mycoses are rare in dogs. As this dog did not show clinical signs of a systemic mycosis and had never stayed in an endemic area, this disease appears unlikely. Moreover, in systemic mycosis the CSF tends to contain predominantly granulocytes (neutrophils, eosinophils) and macrophages.

In human, optic neuritis is a known complication of vaccination for influenza, anthrax or rubella, or natural infection with hepatitis A virus or varicella-zoster virus. Based on detection of immune complexes in the CSF, or retinal or optic nerve autoantibodies, it is assumed that optic neuritis in such patients is caused through immune-mediated demyelination. The dog’s last vaccination was 5 months before the first occurrence of optic neuritis so this pathogenesis seems unlikely in this case.

After interpretation of all findings, we suggest that meningoencephalitis and optic neuritis in the patient we describe were caused by TBEV and the associated immune-mediated response. In endemic areas, TBEV should be considered as a cause of optic neuritis in dogs.

**REFERENCES**
