A Comparison of Combination Therapy (Cyclosporine plus Prednisolone) with Sole Prednisolone Therapy in 7 Dogs with Necrotizing Meningoencephalitis

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\textbf{ABSTRACT.} Administration of immunosuppressive doses of glucocorticosteroids is the traditional primary treatment in necrotizing meningoencephalitis (NME) in dogs. However, response is variable and clinical signs often recur quickly with tapering dosage. Prognosis is poor and long-term therapy causes many complications. In the present study, we compared the long-term effects of combination (cyclosporine plus prednisolone) therapy with sole prednisolone therapy in management in dogs with NME. All NME cases in this study were examined with magnetic resonance imaging and cerebrospinal fluid analysis, and confirmed by histopathologic examination. The mean survival time of combination therapy group was 305.7 ± 94.7 days. The mean survival time of sole prednisolone therapy group was 58.3 ± 30.5 days. This case report demonstrates that combination treatment of cyclosporine with prednisolone is more effective in survival time than administration of only prednisolone in NME cases.

\textbf{KEY WORDS:} canine, cyclosporine, necrotizing meningoencephalitis.

Necrotizing meningoencephalitis (NME) is a unique inflammation disorder of brain in small breed dogs. The disease primarily affecting the cerebral hemispheres has been described in Pug, Maltese, and Yorkshire terrier [6, 9, 12–14]. Even though the cause of this disease is unknown, the brain lesions are quite similar to those of alpha herpes virus meningoencephalitis in human beings [6]. A previous report [9] showed that a certain autoantibody against a canine brain tissue was detected in the cerebrospinal fluid (CSF) and serum, indicating an autoimmune pathology in NME. In addition, one study [13] revealed all tested cases with NME possessed the anti-astrocyte autoantibody.

Administration of immunosuppressive doses of glucocorticosteroids is the traditional primary treatment in NME in dogs [3]. However, response is variable and clinical signs often recur quickly with tapering dosage. Prognosis is poor and long-term therapy causes many complications [3]. In the present study, we compared the long-term effects of cyclosporine plus prednisolone therapy with sole prednisolone therapy in management in dogs with NME.

This report described the clinical findings, imaging characteristics and pathologic features of NME and long-term survival after cyclosporine therapy. To the author’s knowledge, this study is the first report about management of NME using cyclosporine in dogs.

Seven dogs were definitively diagnosed as NME based on magnetic resonance imaging (MRI), CSF analysis, and histopathologic examination. Of the 7 NME cases, 2 dogs were Maltese, 2 dogs were Yorkshire terrier, 2 dogs were Shih-tzu and the other one dog was Pug. Pug dog encephalitis can be classified into one of NME if the intracranial lesions of Pug dog encephalitis are consistent with NME (cavitation, necrosis). Therefore we included Pug dog case in this study.

The onset age of disease was between 1.5 years to 8 years. The most common clinical sign was seizure episode, ataxia and head tilt were also noted. All cases in this study showed acute progression of neurological signs. The clinical signs of 7 dogs were initiated at 1 or 2 day before presentation and progressed severely. This signalment and complaints were obtained from the questionnaire that clients provided to us. Five dogs were female and 2 dogs were male (Table 1).

The 7 NME cases were randomly devided into two groups (4 dogs were cyclosporine plus prednisolone combination therapy group and 3 dogs were prednisolone sole therapy group). There were not significant differences as neurological features of initial course among 2 groups.

To evaluate the intracranial lesions, we performed a brain MRI scan using a 0.2 T unit (E-scan®; ESAOTE, Genova, Italy), and CSF analysis. T1- and T2-weighted images and postcontrast T1-weighted images were obtained on MRI scan. CSF was collected by cerebellomedullary cisternal puncture method with 22 gauge spinal needle. As CSF has a low cellular content, a cytocentrifuge (Cytospin4, Thermo Shandon, London, UK) was employed instead of using a direct smear of CSF. The CSF sample was spun

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directly onto a glass slide at 250 g for 5 min. The slides were immediately dried, stained by the Diff-Quik stain (Sysmex Corp., Kobe, Japan) and examined under light microscopy. All cases revealed mononocytic pleocytosis in CSF analysis. Total CSF protein determination was performed with a urinary reagent dipstick according to a previous method [5]. Results of CSF total protein concentrations in 7 dogs were between 30 mg/dl and 100 mg/dl (reference range; below 30 mg/dl). To rule out canine distemper virus infection and toxoplasmosis, canine distemper virus antigen (RT-PCR) and toxoplasma IgG/IgM (Neodin Vetlab, Seoul, Korea) were tested, and all results were negative for the CSF. In addition, bacterial and fungal cultures were performed on the CSF, and the results were all negative.

Five cases showed multifocal lesions and 2 cases showed focal lesion on MRI findings. Intracranial lesions in all cases showed hypersignal intensities on T1-weighted images and hyposignal intensities on T2-weighted images and not enhanced after intravenous administration of gadolinium-diethylenetriamine pentaacetic acid (Omniscan®; Nycomed, Inc., Princeton, NJ, U.S.A.; 0.1 mmol/kg, IV) (Fig. 1 A and B).

Therapy was initiated after MRI and CSF analysis. Four dogs (case 1, 2, 3 and 4) were managed with prednisolone (Prednisolone; Korea Pharma Co., Ltd., Korea; 1 mg/kg, PO, q 12 hr) and cyclosporine (Implanta; Hanmi Pharma Co., Ltd., Korea; 5 mg/kg, PO, q 24 hr) combination. Two weeks after initial treatment, prednisolone dosage was

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Breed</th>
<th>Age onset (Years)</th>
<th>Sex</th>
<th>Clinical signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Shih-tzu</td>
<td>2.2</td>
<td>F</td>
<td>Seizure, head tilt</td>
</tr>
<tr>
<td>Case 2</td>
<td>Yorkshire terrier</td>
<td>8</td>
<td>M</td>
<td>Seizure, ataxia</td>
</tr>
<tr>
<td>Case 3</td>
<td>Shih-tzu</td>
<td>4</td>
<td>F</td>
<td>Seizure</td>
</tr>
<tr>
<td>Case 4</td>
<td>Maltese</td>
<td>2.5</td>
<td>F</td>
<td>Seizure</td>
</tr>
<tr>
<td>Case 5</td>
<td>Maltese</td>
<td>2</td>
<td>F</td>
<td>Ataxia, head tilt</td>
</tr>
<tr>
<td>Case 6</td>
<td>Yorkshire terrier</td>
<td>5</td>
<td>M</td>
<td>Seizure</td>
</tr>
<tr>
<td>Case 7</td>
<td>Pug</td>
<td>1.5</td>
<td>F</td>
<td>Seizure</td>
</tr>
</tbody>
</table>

F: female, M: male.

Fig. 1. MR images, gross finding and histopathologic findings of the NME in case number 4. A: Transverse T1-weighted image. Multifocal hypointense lesions are notified on cerebral parenchyma (arrows). B: Multifocal hyperintense lesions are also notified on Transverse T2-weighted image from A (arrows). C: Transverse section of the brain at the slice level corresponding to A and B. Multiple necrotic lesions are seen (arrows). D: Severe neuronal necrosis and vacuolation are indentified on histopathologic examination (in cerebral cortex). Hematoxylin and eosin, × 100.
Cyclosporine is the effective therapeutic options for GME in especially lymphocytes, reticulohistocytes and macrophagizations of inflammatory cells, around blood vessels, goencephalitis (GME) in dogs on the basis of the dense D).

Cyclosporine is an important drug in human medicine and was initially used to produce immunosuppression in organ transplant recipients [11]. Recently this cyclic oligopeptide, which is able to block the transcription of cytokine genes in activated T cells, is being increasingly used in veterinary medicine [4]. In veterinary medicine, cyclosporine has been reported to be effective for the treatment of a number of dermatologic diseases and ophthalmologic problems [4, 10, 11]. Recent reports [1, 4] suggested that the cyclosporine is the effective therapeutic options for GME in dogs. However, to the authors’s knowledge, effectiveness of cyclosporine for NME in dogs was not reported until recently.

The etiology of NME is unknown. However, recent studies raised the possibility of an immune mediated pathogenesis for NME cases [7, 13]. To date standard treatment for NME consists of glucocorticoids given at immunosuppressive doses, which may help reduce inflammatory and immune reactions during initial stage of the disease [3]. This results in remission of clinical signs for a period of time, but many dogs require sustained therapy to avoid relapse [3]. Adverse effects such as polyuria-polydipsia, polyphagia, weight gain, hepatotoxicity, iatrogenic hyperadrenocorticism and lethargy are frequently seen during long-term therapy. Thus alternative treatments for NME are required due to these disadvantages [1, 3, 4]. Of the immune suppressive agents, cyclosporine has been focused and it has primarily been used to suppress the immune system of autoimmune diseases, therefore we used this drug for treatment of NME cases. Cyclosporine is a lipophilic peptide with poor blood-brain barrier permeability that may be effectively trapped in the cerebral endothelial cells and the choroids plexuses [1]. Because NME is a perivascular disease as GME, a therapeutic cyclosporine concentration is most likely present in affected areas of the CNS [1, 6, 8].

According to a previous report, cyclosporine is nor nephrotoxic or hepatotoxic in dogs unless extremely high blood concentrations (over 3,000 ng/ml) are maintained [1, 2]. No major adverse effects were associated with long-term cyclosporine administration, except for mild dermatologic changes and transient lymphopenia [1, 2]. In one study [11], at daily doses of 20–30 mg/kg, dogs may uncommonly experience gingival hyperplasia and papillomatosis, vomiting, diarrhea, bacterial cystitis, bacterial skin infections, anorexia, hirsuitism, involuntary shaking, nephropathy, bone marrow suppression and lymphoplasmatoïd dermatosis. However, adverse reactions in dogs to cyclosporine at doses 5 mg/kg/day appear to be rare in same study [11]. In the present report, side effects were not noted after long-term cyclosporine administration. Because combination therapy of cyclosporine can reduce prednisolone dosage of treatment, the major side effects of prednisolone were more diminished than those of high dose prednisolone therapy.

Generally, immunosuppressive glucocorticoid therapy in NME could improve clinical signs for few weeks. Most NME cases were died within 2–3 months inspite the immunosuppressive glucocorticoid therapy. Thus we used cyclosporine plus steroid, because cyclosporine takes several weeks to exert its effect. When combination therapy were used, steroid could improved clinical signs initially, and prolonged effect until cyclosporine exert its effect.

In general, NME varied in age at presentation between 6 months and 7 years. The onset and progression of clinical signs of neurological dysfunction may be acute (2 weeks or less) or chronic (4–6 moths) [6–8]. In particular, Yorkshire terrier with NME have been reported between age 1 and 10 years. All dogs in this study showed acute progression of...
clinical signs (less than 1 week) and the ranges of age at start of disease were between 1.5 years to 8 years.

Generally, the prognosis for NME is poor to grave. However, 3 dogs after prednisolone therapy were died within 3 months in this study and 4 dogs after combination therapy showed longer survival time than sole prednisolone therapy.

In conclusion, this report demonstrated that combination treatment of prednisolone with cyclosporine is more effective in survival time than administration of only prednisolone in NME cases.

ACKNOWLEDGMENT. This work was supported by the Konkuk University and the SRC/ERC program of MOST/KOSEF (R11–2002–103).

REFERENCES