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Clinical Communication

Post-vaccinal distemper encephalitis in two Border Collie cross littermates

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Abstract

CASE HISTORY: One 4.5-month-old male Border Collie cross presented with aggression and seizures in October 2006. A 16-month-old, female, spayed Border Collie cross presented with hypersalivation and a dropped jaw and rapidly became stuporous in September 2007. The dogs were littermates and developed acute neurological signs 5 and 27 days, respectively, after vaccination with different modified live vaccines containing canine distemper virus.

HISTOPATHOLOGICAL FINDINGS: Sections of brain in both dogs showed evidence of encephalitis mainly centred on the grey matter of brainstem nuclei, where there was extensive and intense parenchymal and perivascular infiltration of histiocytes and lymphocytes. Intra-nuclear and intra-cytoplasmic inclusions typical of distemper were plentiful and there was abundant labelling for canine distemper virus using immunohistochemistry.

DIAGNOSIS: Post-vaccinal canine distemper.

CLINICAL RELEVANCE: Post-vaccinal canine distemper has mainly been attributed to virulent vaccine virus, but it may also occur in dogs whose immunologic nature makes them susceptible to disease induced by a modified-live vaccine virus that is safe and protective for most dogs.

KEY WORDS: Dog, canine distemper, encephalitis, IHC, vaccine

Introduction

Post-vaccinal encephalitis has been recognised following the administration of certain strains of attenuated canine distemper virus vaccine but published cases are rare (Hartley 1974; Bestetti et al. 1978; Cornwell et al. 1988; McCandlish et al. 1992; Martella et al. 2011). A reversion to virulence by the vaccine virus has been proposed for some of these cases, and Appel (1978) demonstrated reversion to virulence in the laboratory although the reversion in those dogs was not fatal and did not lead to encephalitis.

Post-vaccinal distemper encephalitis was produced experimentally in dogs given modified live vaccine containing distemper virus followed by challenge with virulent parvovirus 3 days later (Krackowka et al. 1982). The mechanism for the development of encephalitis in these dogs was speculated to be due to immune suppression from canine parvovirus infection.

This report describes the occurrence of post-vaccinal distemper encephalitis, 1 year apart, in two littermates that received different live vaccines. A congenital immune defect was a possible reason for the development of the encephalitis.

Clinical history

Case 1

On 14 October 2006 a 4.5-month-old, male Border Collie cross was presented with aggression and seizures; it was subject to euthanasia 4 days later. The dog had been vaccinated with Canvac 4 and Canvac BB (Pfizer Animal Health, Auckland, NZ, now Zoetis Inc., Florham Park, NJ, USA) on 07 September 2006 and given a booster vaccination on 09 October 2006, 5 days before its presentation. Canvac 4 contains live, attenuated strains of canine parvovirus, canine distemper virus, canine adenovirus, and canine parainfluenza virus, while Canvac BB is a killed vaccine for Bordetella bronchiseptica with adjuvant.

Case 2

On 10 September 2007 a 16-month-old, female, spayed Border Collie cross was presented for veterinary examination with hypersalivation and a dropped jaw. Within 24 hours the dog was stuporous and it was subject to euthanasia on 12 September 2007. On 14 August 2007, approximately 1 month prior to presentation, the dog had received an annual booster with Vanguard Plus 5 (Pfizer Animal Health) containing live attenuated parvovirus, canine distemper virus, canine adenovirus, and canine parainfluenza virus. The dog had been initially vaccinated 1 year before on 18 July 2006 and booster vaccinated on the 10 August 2006 with Canvac 4 and Canvac BB.

Subsequent investigation revealed that these two dogs were littermates owned by different families in the Rangiora area of North Canterbury, New Zealand. The dogs had a mixed lineage including Border Collie (dam of mother) and Airedale crossed with perhaps Labrador or Great Dane (father of mother). The mother of the dogs had been mated back to her father.

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PBS Phosphate buffered saline
Histopathological findings

Fresh brain tissue and brain fixed in 10% formalin was received from each dog, and fixed heart, kidney, liver and lung from Dog 1. There were no gross lesions. The fixed material was routinely processed and microscopic sections were cut at 4 µm and stained with H&E.

Case 1

There were no lesions in the heart, kidney, liver or lung. In the brain, lesions were present in the cerebral cortex, thalamus, midbrain, medulla and cerebellum. The cerebral cortex had occasional, small, random foci of lymphocytes and microglial cells in the white and grey matter. One focus had a few cells with eosinophilic, cytoplasmic inclusions but most did not. Occasional individual or clusters of four to six cysts resembling *Toxoplasma* or *Neospora* spp. were present in the grey matter of the cerebral cortex. Most of the cysts were separate from the small, inflammatory foci; one cyst was present within an inflammatory focus.

The most severe lesions were in the grey matter of the thalamus where there was extensive and intense parenchymal and perivascular infiltration of histiocytes and lymphocytes. The grey matter in the dorsal midbrain at the level of the rostral colliculus was infiltrated with lymphocytes. The medulla had a few, small, focal areas of lymphocytes and microglial cells in the grey matter, and the cerebellum had several, small, focal areas of granular cell apoptosis with vacuolation of the adjacent white matter and hypercellularity of the adjacent molecular cell layer. Nuclear and cytoplasmic eosinophilic inclusions were present in large numbers in neurons and in lesser numbers of glial cells in the thalamus (Figure 1), and they were also present in large numbers in the dorsal midbrain, and within ependymal cells of the mesencephalic aqueduct contiguous with an area of affected thalamic grey matter.

Case 2

There were no lesions in the cerebrum and lesions were present in the cerebellum and in the brainstem from the rostral thalamus to the medulla. The lesions in the brainstem mainly involved the grey matter and the immediately adjacent white matter and consisted of parenchymal infiltrates of lymphocytes and histiocytes with perivascular lymphocytes. Eosinophilic nuclear and cytoplasmic inclusions occurred in neurons and glial cells. The inclusions were plentiful in some areas, and absent or few in others. There were also scattered eosinophilic shrunken neurons with pyknotic nuclei and many other pyknotic cells.

Immunohistochemistry

Immunohistochemistry was performed on samples from both cases. Formalin-fixed, paraffin-embedded tissue sections, that were 4 µm thick, were mounted on charged slides, and air-dried overnight at 37°C. Sections were deparaffinized through xylene to 100% reagent alcohol, and then treated with 0.3% hydrogen peroxide in 100% methanol for 30 minutes. Sections were rehydrated to water through 95% and 70% reagent alcohols.

Antigen retrieval was performed with heat-induced epitope retrieval for 30 minutes at 95°C, followed by a 20-minute cool down. The retrieval solution was Target Retrieval Solution, pH 6 (Dako Corp, Carpinteria, CA, USA). After antigen retrieval, slides were rinsed in deionised water and placed in 0.1 M phosphate buffered saline (PBS), pH 7.4. Slides were then incubated with blocking reagent (PBS with 0.02% Tween-20 and 10% normal horse serum) and blocked for 20 minutes. Monoclonal mouse anti-canine distemper virus (CMI 2–12; Custom Monoclonals International, Sacramento, CA, USA) was diluted at 1:200 in PBS with 0.02% Tween-20 and 10% normal horse serum and blocked for 20 minutes. Monoclonal mouse anti-canine distemper virus (CMI 2–12; Custom Monoclonals International, Sacramento, CA, USA) was diluted at 1:200 in PBS with 0.02% Tween-20, and slides were incubated for 1 hour at room temperature. Dako Envision +System-HRP (Dako Corp), used according to the manufacturer’s instructions, was applied for 30 minutes to label mouse anti-anti-canine distemper virus. Sections were counterstained in Mayer’s haematoxylin and air dried. Canine cerebellum from a case of natural distemper in California was used as a positive control. Negative controls were performed by using duplicate sections in which isotype serum was used in place of the primary antibody.
Case 1
Immunohistochemistry was performed on blocks that included thalamus, midbrain and medulla. There was marked cytoplasmic and nuclear labelling with antibody to canine distemper virus of neuronal cell bodies and their processes and of glial cell nuclei in the grey matter of the thalamus (Figure 2), in cells in parts of the ependyma of the thalamus, in the dorsal midbrain grey matter, ventral midbrain meninges, and in occasional, scattered cells in the white matter of the medulla.

Case 2
Immunohistochemistry was performed on a block that included midbrain and cerebellum. There was marked cytoplasmic and nuclear labelling with antibody to canine distemper virus of neuronal cell bodies and their processes and of glial cell nuclei in the grey matter of the midbrain. There were scattered small areas of labelling of cells and their processes in the cerebellar granular and molecular cell layers. The nuclei and cytoplasm of cells in parts of the meninges of the ventral midbrain also labelled intensely.

Discussion
The lesions and epidemiological features suggest that the encephalitis in these dogs was the result of infection with distemper vaccine virus rather than being due to a field strain infection for several reasons. First, canine distemper is an exceedingly rare disease in New Zealand, assisted by the absence of wildlife reservoirs such as raccoons (*Procyon lotor*), and over the last 30 years most practitioners have never seen a case. The chances of two littermates that had lived apart for over a year selectively developing natural distemper seems remote especially as no other cases of distemper were recognised in the dog population at the time and none have been reported since then. Second, the encephalitis developed soon after vaccination. Third, the lesions were similar to those described by Hartley (1974) for encephalitis in dogs associated with a batch of canine distemper (Rockborn) vaccine. Affected dogs were of six different breeds, from 10 to 20 weeks old, and developed clinical signs 8–18 days post vaccination. These episodes were attributed to an unusually virulent vaccine virus.

Although the histological lesions in the dogs in our report are similar to those described by Hartley (1974) we believe the encephalitis in our two dogs was likely due to a congenital susceptibility, rather than a problem with the vaccine. A common environmental influence on the dogs’ immune systems is possible but unlikely given that the dogs had lived in separate homes for over a year.

There are reports in the medical literature attributing immunodeficiency as the underlying reason for vaccine-induced disease. This includes encephalitis after vaccination for the measles virus in a child with profoundly low numbers of CD8 T lymphocytes who was clinically normal and whose presumed immunodeficiency went undetected (Bitnum et al. 1999). Cases of severe primary immunodeficiency in children are usually detected before vaccination, so vaccination of such children with live vaccine is avoided, thus making the occurrence of post-vaccinal measles encephalitis even rarer than might otherwise be the case (Bitnum et al. 1999).

Hartley (1974) described two episodes of post-vaccinal distemper encephalitis affecting large numbers of dogs in Australia in the late 1960s and early 1970s. The dogs had been vaccinated with a distemper/hepatitis vaccine. Affected dogs were of six different breeds, from 10 to 20 weeks old, and developed clinical signs 8–18 days post vaccination. These episodes were attributed to an unusually virulent vaccine virus.

Although the occurrence of fatal encephalitis may raise the issue of the safety of live vaccines for some veterinarians. While distressing for the owners of affected dogs, others would argue that these vaccines are highly efficacious and safe for the vast majority of dogs, and without such good vaccines the animal welfare issues arising from periodical distemper epidemics or even low-level endemic distemper infection would be far worse.

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