Subacute necrotising encephalopathy in an Alaskan husky

A 29-month-old female Alaskan husky was presented recumbent, tetraparetic and in a state of dementia, with blindness and cranial nerve deficits. The dog’s progress was followed for over two months, as the signs resolved to a non-progressive mild hypermetria with slight proprioceptive ataxia, a diminished menace response and inability to prehend food. Magnetic resonance imaging (MRI) revealed bilateral cavitation extending from the thalamus to the medulla, with less pronounced degenerative lesions in the caudate nucleus, putamen and claustrum. Cerebrospinal fluid lactate and pyruvate concentrations were in their normal ranges. Necropsy and histological examination confirmed the MRI findings as well as neuronal degeneration of the cerebellar cortex in the vermis and degenerative changes in the neocortex at the depths of the cerebral sulci. In view of the similarity of lesions to subacute necrotising encephalomyelopathy, known as Leigh’s disease in humans, a tentative diagnosis of a mitochondrial encephalopathy was made.

INTRODUCTION

Generalised non-inflammatory degenerative encephalopathies in small animals are often due to toxins, ischaemia and rare storage diseases (Summers and others 1995). There are only a few degenerative encephalopathies that appear to be due to true metabolic energy deficiencies, such as an inability to generate adenosine triphosphate (ATP). These metabolic encephalopathies resemble ischaemic responses histologically, with an abnormal distribution of lesions. To date, only two presumpitive energy (ATP) deficiency metabolic encephalopathies have been identified in the veterinary literature which are not disorders in amino acid metabolism (Brenner and others 1997a,b). These presumptions were based on electron microscopy, which revealed changes in mitochondria of glial cells in both the Australian cattle dog encephalomyelopathy and the springer spaniel encephalopathy.

The present report describes the clinical findings in one of 12 Alaskan huskies known to have been affected with a subacute necrotising encephalopathy (SNE), which is similar to a mitochondrial encephalomyelopathy in humans known as Leigh’s disease (Lewis 1965, Greenhouse and Schneck 1968, Hardman and others 1968, Richter 1968).

CASE HISTORY

A two-and-a-half-year-old female Alaskan husky was referred to the Cornell University Companion Animal Hospital with a history of an acute onset of cluster seizures for a few hours, followed by lateral recumbency and tetraplegia two days before referral. A peculiar gait had been noted at six months of age by the owners, with no apparent ataxia or proprioceptive deficits. The abnormal gait had only been noticed when the dog had participated as part of a sled dog team, where the animal appeared less agile than the other dogs, especially when turning corners.

At the time of admission, the dog was in lateral recumbency and unable to rise. The case was poorly responsive and acted dazed or sedated. When picked up, all four limbs were rigidly extended, as were the trunk and neck. No voluntary movement was initiated.

On manipulation, all four limbs were very hypertonic and patellar reflexes were brisk. Flexor reflexes were intact, but nociception from the digits of all four paws and the face was depressed, especially in the nasal mucosa. The dog did not appear to recognise anything in its environment and had no menace responses. The pupils were normal in size and response to light. During this time the dog could not eat and was supported with intravenous dextrose and lactated Ringer’s solution to maintain hydration status.

After five days the dog could stand and walk, but was very ataxic and easily lost its balance and fell. The animal had no postural reactions and still had facial
hypalgesia. Menace responses were still absent, yet nociception in the limbs was regained. The swallowing reflexes were intact and the dog could be syringe-fed slowly, but was still unable to prehend food or water voluntarily.

Ten days after admission the dog exhibited a propulsive gait with marked hypermetria of the thoracic limbs and moderate hypermetria in the pelvic limbs. This consisted of a repetitive overflexion in a stereotyped fashion without dysmetria or balance loss. Postural reactions were still very delayed and facial hypealgesia was still present. Although the dog still had no menace response, it followed its attendant visually around the room. It could not prehend food, but could be syringe-fed to maintain adequate nutritional status.

By day 14 after the onset of tetraplegia the animal exhibited very little ataxia, with minimal proprioceptive deficits, a propulsive gait, moderate hypermetria and an inability to prehend food. The dog began to display a menace response in both eyes (stronger in the right) and remained in this static state for the next two months of observation, except for one episode of seizures. At this time euthanasia was performed.

Two weeks after the initial recumbency, magnetic resonance imaging (MRI) had been performed showing the changes seen in Fig 1 A. In the T2-weighted images (Fig 1 A to D) the lesions can be seen as hyperintense areas. The most prominent lesion was a bilateral hyperintensity in the centre of the brainstem, extending from the thalamus to the medulla. There were also less intense hyperintensities seen in the putamen, caudate nucleus and claustrum. T1-weighted images showed a non-enhancing bilateral hypointensity in the brainstem, especially the thalamus and midbrain.

Routine serum biochemistry and complete blood count were normal upon presentation to Cornell. Serum pyruvate and lactate concentrations were within normal limits. In the light of recent literature suggesting that metabolic encephalopathies may only show abnormalities in lactate, pyruvate and lactate to pyruvate ratios in the cerebrospinal fluid (CSF), CSF was obtained at the time of euthanasia (Poggi-
The pathological diagnosis was SNE. On the basis of pathological and clinical findings it was hypothesised that the generalised encephalopathy was due to a metabolic defect, presumably at the level of the mitochondria.

**DISCUSSION**

Similar encephalopathies have been identified in the Swaledale lamb and Simmental cattle (Steffen and others 1994, Olby and others 1997). There have been 12 other confirmed cases of this SNE in the Alaskan husky. The first cases in 1992 were from a kennel of racing sled dogs in Minnesota where three litters (one of five pups, two of four pups, and one of two pups) from the same sire or grand sire and related dams produced four puppies with SNE. The age of onset was between six and nine months. The diagnosis in two of these dogs was confirmed by necropsy at the University of Minnesota, with brain pathology evaluated at Cornell University by one of the co-authors (AD). The clinical signs started with ataxia with hypermetria, which progressed. Eventually, two of the four affected dogs were seen at Cornell with general signs of ataxia with hypermetria, proprioceptive deficits, dementia, compulsive ambulation, inability to prehend food and a lack of menace response. One dog also displayed facial hypalgesia.

In 1997, three dogs from a litter of six from Massachusetts were found to have SNE on pathological examination at Cornell. These dogs were presented at between eight and 18 months of age and were primarily found to have isolated seizures which progressed to hypermetric ataxia and lack of a menace response. The degree of alteration in the sensorium of these three cases varied remarkably from the previous dogs from Minnesota. The dogs from Minnesota lacked sensorium, while the dogs from Massachusetts...
would follow their attendant around the room and could still prehend food.

Similar gross and histological lesions were found in a five-month-old dog of a litter of two from a kennel in Wyoming. This dog displayed progressive ataxia with hypermetria and was euthanased.

The latest age for onset of signs was in a six-year-old Alaskan husky from Maine, which was euthanased after initial signs and had similar histopathological lesions when studied by one of the present authors (AD).

In Alaska, two dogs from a litter of two were affected at between six and eight months of age. They showed progressive ataxia with hypermetria, and the lesions were confirmed on histopathological examination (AD). The dog of the present report and its full sister were from a litter of six raised in Alaska; both displayed seizure-like activity three months apart at 26 and 29 months of age, which was followed by lateral recumbency, vocalisation and tetraplegia. Computed tomography was performed on the 26-month-old sister in Alaska and demonstrated pronounced bilateral cavitation in the thalamus (Fig 4).

SNE appears to be a hereditary disease in the Alaskan husky which is recognised by the identification of bilateral thalamic cavitation, which is characteristic of this rare entity. There does not appear to be any direct linkage shared between the kennels with affected dogs. Many of the pedigrees affected go back to very prominent kennels established in Alaska in the 1950s and 1960s. The most intriguing genetic question is whether this disease is inherited through autosomal patterns or through mitochondrial DNA (mtDNA) inheritance.

Mitochondria have their own circular DNA which is made up of just over 16,000 base pairs and contributes 13 subunits to the respiratory chain, two ribosomal RNAs and 22 transfer RNAs, all of which play an integral part in energy production (Sparraco and others 1993, Johns 1995, Adams and Turnbull 1996). All other proteins needed for energy production are made from nuclear DNA and are transported into the mitochondria. This mtDNA can only be found in the oocyte; therefore, any zygote formed will have mtDNA from the mother – hence maternal inheritance (Lightowers and others 1997).

Another caveat to mitochondrial inheritance is the fact that the number of mutant mitochondria within a cell can vary due to unequal segregation of mitochondria during cell division. This process of unequal segregation is called heteroplasmy. Therefore, through heteroplasmy, different tissues of the body can have marked variability in the numbers of mutated mtDNA, resulting in clinical signs related to the organ systems with the highest proportion of mutated mitochondria.

It is believed that there is a threshold effect owing to heteroplasmy which allows for differences in age of onset, clinical signs and progression of the disease (DiMauro and Morales 1993, Johns 1995, Zeviani and others 1998). For example, a clinically affected dog may have 85 per cent of mitochondria with a specific mutation in the oligodendrocytes, while a sibling may only have 60 per cent mutated mtDNA and not exhibit clinical signs, but may develop clinical signs later in life due to functional deficits of the mitochondria and further cell divisions.

In the Alaskan husky, the percentage of affected dogs varies between 20 and 100 per cent in a litter, which suggests a mitochondrial pattern of inheritance with heteroplasmy, yet the larger litters tend to have a lower occurrence of the disease much like the case of an autosomal pattern of inheritance (25 to 50 per cent).

It is assumed that the only mtDNA defects that can lead to mitochondrial dysfunction are deletions, point mutations and duplications in the DNA, much like nuclear DNA (nDNA) (DiMauro 1996).

Considering that mtDNA only makes a fraction of the machinery needed for mitochondrial function, one would assume that only a small portion of the defects in mitochondrial function would be directly related to mtDNA. Unfortunately, unlike nDNA, mtDNA does not have 'proof-reading' mechanisms; therefore, mutation of mtDNA is far more likely to occur. Alternatively, the number of mutations that can occur in nDNA far outweighs the number of mutations that can occur in mtDNA, taking into account that nDNA encodes for far more of the enzymes and translocases (ie, defects in transport, substrate utilisation, Krebs cycle, electron transport, and so on), protein importation mechanisms and intergenomic signalling proteins (DiMauro 1996).

In recent years, work on Leigh's disease and similar encephalomyopathies in humans has identified a number of defects in mtDNA. Mutations in the cytochrome c oxidase, NADH dehydrogenase and ATPase genes of the mtDNA have been identified as causes of Leigh's disease (DiMauro and others 1987, Van Coster and others 1991, Degoul and others 1995, 1997, DiMauro and De Vivo 1996, Morris and others 1996). The only prevalent chromosomal mutation leading to Leigh's disease is the E1 alpha subunit mutation of the X chromosome (DiMauro and De Vivo 1996, Robinson and others 1996). Even though all of these mutations have been identified, they have only been confirmed as the cause of disease in about 50 per cent of Leigh's disease cases (Rahman and others 1996).

In veterinary medicine, the abilities to investigate these diseases are in their infancy and still confined to biochemical analysis and neuroradiological findings. In the human literature, there are suggestions that chronological MRI scans can show progression of necrotic lesions in commonly affected areas of the brain, with calcification in chronically affected areas (van der Knapp and others 1996, Valanne and others 1998).

Unfortunately, MRI used in this way is usually a prohibitively costly approach. Therefore, it would be most effective to try to identify mitochondrial disorders biochemically through serum and CSF lactate, pyruvate and alanine concentrations. Literature suggests that these neuropathological disorders can produce serum eleva-
tions which are often mild to moderate in magnitude. However, in human patients with pure encephalopathies of mitochondrial derivation there were elevations in CSF lactate and/or pyruvate that were not evident in the serum (Jackson and others 1995, Zeviani and others 1996). Therefore, it may be more rewarding to collect CSF for evaluation of the metabolic status of the nervous system.

Unfortunately, these diseases sometimes show no detectable metabolic abnormalities either in the CSF or the serum (Jackson and others 1995). With regard to the present results, it can be safely assumed that there are no apparent abnormal increases in CSF lactate or pyruvate concentrations; in fact they may be slightly decreased. It would be ideal also to evaluate CSF lactate and pyruvate before the onset of clinical signs. Considering the extent of the lesion seen in SNE, it is likely that tissues that were once metabolically compromised may have degenerated. Further investigation into canine CSF lactate and pyruvate concentrations are needed to make more educated conclusions regarding normal compared with abnormal values of these parameters.

Various treatments of the mitochondrial encephalopathies have tended to be quite unrewarding. The only current treatment (at the time of writing) involves dietary change and ergogenic supplements. In cases of disorders in the Krebs cycle, a ketogenic diet can be of benefit. Supplementing various quantities of B vitamins, vitamin E and other ergogenic aids, such as coenzyme Q and succinate, has been met with limited success in a few cases (van Erven and others 1987, Calvani and others 1993). Up to the time of writing, therapeutic attempts with ergogenic supplements had not yet been used in any cases of SNE in dogs.

Conclusions
Mitochondrial diseases have begun to be recognized and categorized in human medicine over the past 10 years. It is assumed that the same groups of diseases will probably occur in other mammals. It is hoped that with proper biochemical screening more and more of the idiopathic neurological syndromes will be identified as metabolic encephalopathies, which may be linked to specific mitochondrial abnormalities.

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References