Narcolepsy in a hypocretin/orxin-deficient chihuahua

M. Tonokura, K. Fujita, M. Morozumi, Y. Yoshida, T. Kanbayashi, S. Nishino

A two-year-old male chihuahua suffered attacks of muscle weakness and immobility, although it had no family history of paroxysmal attacks. No neurological or blood biochemical abnormalities were recorded when it was first examined. The attacks were typically elicited by stimulation, such as feeding, and a case of sporadic narcolepsy-cataplexy was therefore suspected. Treatment orally three times a day with 1 mg/kg imipramine, was effective in reducing the attacks. The concentration of hypocretin-1/orxin A in the dog’s cerebrospinal fluid was less than 80 pg/ml (22:5 pmol/litre), compared with normal canine levels of 250 to 350 pg/ml (70-0 to 98-3 pmol/litre), supporting a diagnosis of hypocretin-deficient narcolepsy.

NARCOLEPSY is a disabling sleep disorder characterised by excessive daytime sleepiness, cataplexy, that is, a sudden loss of muscle tone induced by excitation, and rapid eye movement (REM) sleep-related abnormalities (Nishino and Mignot 1997, Nishino and others 2000). The disorder affects 0-02 to 0-18 per cent of the human population, and there are both sporadic (95 per cent) and familial (5 per cent) forms of the disorder. Sporadic and familial cases of narcolepsy have also been reported in dogs (Nishino and others 2000), which have short sleep latencies, fragmented sleep patterns and cataplexy (Nishino and Mignot 1997, Nishino and others 2000). Abnormal sleep patterns are not a serious problem in dogs, but cataplexy is disabling. As in human narcolepsy, cataplexy in canine narcolepsy is often triggered by stimulation, for example, by the presentation of food or by play. The prevalence of canine narcolepsy is not known, but sporadic disease has been reported in 17 breeds (Baker and others 1982, S. Nishino and others, Veterinary Record (2003) 152, 776-779).

References

ACCUROC (1997) Nonparametric receiver operating characteristics analysis, version 3.2. Montreal, Canada, Accumetric Corporation


unpublished observations) and familial cases have been reported in three breeds (Hungs and others 2001). The canine model of narcolepsy has contributed to the recent discoveries about the pathogenesis/pathophysiology of narcolepsy, and it is now known that it is associated with a deficit in hypocretin/orexin neurotransmission. Mutations in hypocretin receptor 2 were found in the familial form (Lin and others 1999) and losses of hypocretin peptides were observed in sporadic canine narcolepsy (Ripley and others 2001) and in most human narcoleptics (Peyron and others 2000, Nishino and others 2001). This paper describes a case of sporadic hypocretin-deficient narcolepsy in a chihuahua.

CASE REPORT

A two-year-old male chihuahua, weighing 1.3 kg, occasionally had attacks of immobility while consuming a particularly appetising meal; a sudden buckling of the knees and dropping of the neck was also observed regularly when it attempted to feed. The dog had no past or present medical history, and its parents and siblings were not affected in the same way. No physical or neurological abnormalities were found when it was examined, and its haematological and blood biochemical parameters were in the normal range. Its blood ammonia was normal, both before and two hours after a meal, and its total bile acids were moderately high both before (73.6

First attack of immobility

Cataplexy (elapsed time [minutes] during a meal)

Imipramine (mg/kg/day)

Bodyweight (kg)
Biochemical findings and repeated clinical examination revealed no abnormal blood biochemical findings and no signs of a portosystemic shunt were observed. The immunoglobulin M antibody titre for canine distemper virus was negative. An electrocardiogram revealed no sign of abnormalities, and no abnormalities were observed on thoracic skull and abdominal radiographs.

Behavioural observations revealed that feeding easily and repeatedly elicited the dog’s attacks of immobility. The muscles of its neck and limbs were weak and it often collapsed to the floor (Fig 1). The attacks lasted for a few seconds to several minutes. During the attacks, the dog’s eyes were open, and no significant changes in its heart and respiration rates were observed. The attacks were easily interrupted by stimuli such as calling the dog’s name or patting its body, and the dog got up immediately and behaved normally with no confusion. REMs were often observed during the long attacks. Despite the repeated attacks, the dog could continue eating and eventually finish its food. It did not salivate and was never incontinent. The attacks also occurred when it was playing with other dogs, while it was being held by its owner, and after it became angry and threatened other dogs.

On the basis of these clinical observations and laboratory findings, narcolepsy-cataplexy was suspected. Because tricyclic antidepressants have been used successfully for cataplexy in dogs and human beings (Nishino and Mignot 1997), the dog was treated orally, three times a day with 1 mg/kg imipramine. As a result, the number of cataplectic attacks gradually decreased, and the dog took a much shorter time to finish its food with the medication; its average time to finish a meal had been reduced by 75 per cent one week after initiating the treatment (Fig 2).

With the owner’s permission, a sample of cerebrospinal fluid (CSF) was taken from the dog 13 weeks after the first examination. The dog was anaesthetised and 0·7 ml of CSF was collected from the cisterna magna by the method described by Ripley and others (2001). The sample was clear, it contained no more than 5 mononuclear cells/mm³, and its protein and glucose levels were in the normal ranges (0·3-6 g/litre and 3-4 2·5 g/litre, respectively) by the enzymatic method. Hypocretin-1 was measured in the non-extracted CSF with a radioimmunoassay kit (Phoenix Pharmaceutical) as described by Ripley and others (2001). The hypocretin concentration was undetectable low (<80 pg/ml [22·5 pmoI/litre]), whereas the normal canine levels, established in five different breeds, range from 250 to 350 pg/ml (70-0 to 98·3 pmoI/litre). This result indicated that the dog was suffering from hypocretin-deficient narcolepsy (Ripley and others 2001).

Further physical and neurological examinations were carried out every two weeks, but no abnormalities were found. During this period, the appetite of the dog increased, and it ate the food left by another chihuahua kept at the same home. After nine weeks of imipramine treatment, the dog’s body weight had increased by 15 per cent to 1·5 kg (Fig 2). Could be interrupted by various stimuli, such as calling the dog’s name or patting its body. It was therefore suspected that the dog was affected by cataplexy associated with narcolepsy. Imipramine, one of the tricyclic antidepressants, had been reported to be effective in human and canine narcolepsy (Nishino and Mignot 1997). Tricyclic antidepressants potently reduce REM sleep and cataplexy, but have no effect on most seizures or exacerbate them (Baldessarini 1985). The fact that the dog responded to imipramine treatment further suggested that the attacks of immobility were cataplexy.

It has now been shown, by a series of experiments on cases of spontaneous canine narcolepsy and in a model of narcolepsy in genetically modified mice, that a deficiency in hypocretin neurotransmission is involved in the pathophysiology of narcolepsy (Chemelli and others 1999, Lin and others 1999, Ripley and others 2001). Hypocretins are hypocretin-deficient narcolepsy. In humans and mice, hypocretin deficiency has been found in cases of narcolepsy in dobermanns, labradors and dachshunds (Lin and others 1999, Hungs and others 2000), and hypocretin peptide deficiency was demonstrated in the CSF and brains of a few sporadically narcoleptic dogs tested (Ripley and others 2001). In general, the clinical signs first appear in genetically narcoleptic dogs at between four and 24 weeks of age, whereas in sporadically narcoleptic dogs they appear later, between seven and seven years (Baker and others 1982, Riehl and others 1998).

This chihuahua the attacks began when it was two years old and, because it had no family history of narcolepsy-cataplexy, hypocretin-deficient narcolepsy was suspected. A measurement indicated that the concentration of hypocretin in its CSF was significantly below the normal range for dogs. Recent human studies have demonstrated that a deficiency of hypocretin in the CSF is highly specific for narcolepsy-cataplexy, differentiating it from various other neurological and sleep disorders (Ripley and others 2001, Mignot and others 2002).

After the onset of the disease, significant increases in the dog’s appetite and body weight were observed. It is known that cases of narcolepsy due to a deficiency of hypocretin in human beings and mice become obese, regardless of any treatment for the narcolepsy, suggesting that there is a change in energy homeostasis in hypocretin-deficient narcolepsy (Hara and others 2001, Nishino and others 2001). A reduction in food intake and a reduction in metabolic rate have been observed in human beings and mice with narcolepsy (Lammers and others 1996, Hara and others 2001, Nishino and others 2001), but an increase in appetite at the onset of the disease has also been observed in some human cases (S. Nevsimalova, personal communication). Thus, the obesity observed in this chihuahua may also be related to rapid changes in its hypocretin status.

Narcolepsy is neither a progressive nor a life-threatening disease, but the clinical signs persist throughout life (Nishino and Mignot 1997). The establishment of a definitive diagnosis by the measurement of hypocretin in CSF will help to determine the prognosis and treatment. A plan for the daily care of this chihuahua has been established with the owner. It is provided with a soft sleeping mat, glass feeding containers are not used, its water container is placed above shoulder level, and it is fed a low-calorie diet. This plan, together with anticonvulsant medication, will be continued for the life of the dog, to maintain its quality of life.
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References


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Pathology of bovine tuberculosis in the European wild boar (Sus scrofa)

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BOVINE tuberculosis (TB), caused by infection with Mycobacterium bovis, is one of the most important re-emerging zoonotic diseases in Europe. It has been described in the European wild boar (Sus scrofa) (Bollo and others 2000), and molecular epidemiological data suggest interspecies transmission between wild boar, cattle and deer (Aranzaz and others 1996). Wild boar populations are increasing and expanding in Europe (Sáez-Royuela and Telleria 1986), and are likely to play an important role in the epidemiology and control of TB within endemic areas. However, little information has been published on the pathology in this species. This short communication describes for the first time the morphology and distribution of bovine TB lesions in the wild boar.

The animals included in this study were 53 free-living wild boar shot during the hunting season in southern Spain. They presented with gross lesions compatible with TB, from which M bovis infection was confirmed by culture in Lowenstein Jensen medium with the addition of pyruvate, and identified by PCR.

All of the animals had gross tuberculomas lesions in the mandibular lymph nodes (Fig 1). The bronchial, mediastinal and mesenteric lymph nodes were also frequently affected. The thoracic lymph nodes had lesions in 56 per cent of the cases and there were lesions in the abdominal lymph nodes in 49 per cent. One-third of the cases (34 per cent) had macroscopical lesions exclusively located in mandibular lymph...
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