Tremorgenic mycotoxicosis and ongaonga poisoning: Brief case studies

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The peracute onset of tremors and ataxia in dogs are commonly encountered in New Zealand companion animal veterinary practice. Potential causes include intoxication; metabolic disease such as hypocalcaemia and hypoglycaemia; inflammatory disease; vascular disease; trauma and neoplasia (Nelson *et al.* 2003).

The following case studies describe two less commonly recognised toxicities occurring in New Zealand presenting with ataxia and tremor as primary clinical signs. The true incidence of these poisonings may be underestimated. Both respond to symptomatic treatment and are without definitive diagnostic testing. They both need to be considered in the differential diagnosis list of acute onset of tremor in New Zealand dogs.

Tremorgenic mycotoxicosis in a dog

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Introduction

Toxins that cause tremor and ataxia include tremorgenic mycotoxins, metaldehyde, organophosphates, carbamates, permethrins, methylxanthines, flouroacetate, strychnine, zinc phosphide and drugs of abuse (Walter 2002, Nelson *et al.* 2003). Whilst in many cases of intoxication presenting with tremor and ataxia signs can be attributed to exposure to a specific poison, it is the author's experience that in some cases the toxin remains unidentified. The free-ranging lifestyle of many rural New Zealand dogs with their ready access to decaying organic matter and the dogs' propensity to eat it, makes mycotoxin ingestion a possible explanation for these otherwise unknown intoxications.

Tremorgenic mycotoxins have been identified as a cause of peracute tremor and ataxia in dogs although there are few published reports (Hocking *et al.* 1988, Walter 2002, Young *et al.* 2003, Munday *et al.* 2008, Eriksen *et al.* 2010). The condition is considered to be 'not uncommon' by the Animal Poison Control Center of the American Society for the Protection of Animals (Schell 2000) but only two previous cases have been reported in New Zealand (Munday *et al.* 2008). The disease is not described in the 3rd edition of the New Zealand text Veterinary Clinical Toxicology (Parton *et al.* 2006). Lack of published information and consequent awareness coupled with diagnostic difficulties may allow this condition to remain under-diagnosed and the true incidence could be much higher.

This case report describes the history, clinical findings, and treatment of a dog with a presumptive diagnosis of tremorgenic mycotoxicosis from ingestion of mouldy cream cheese.

Signalment and clinical signs

An otherwise healthy two year old de-sexed female Maltese terrier with a free ranging lifestyle from a rural home was noticed by the owner to suddenly become disorientated progressing to generalised tremor and ataxia. Signs began approximately thirty minutes after the dog was noticed near the farm rubbish tip.

On presentation for veterinary care, the dog was showing marked tremors, tonic clonic muscle spasm and salivation. There was mild hyperthermia (39.8 C) and mydriasis. There was hyperaesthesia demonstrated by a worsening of signs by the noise of clippers. Signs appeared very similar to metaldehyde intoxication although there was no known access. Without a definitive diagnosis, symptomatic treatment was initiated on the presumption of an unknown toxicity, based on the peracute onset of typical clinical signs and ruling out other likely causes.

Intravenous fluid therapy with Lactated Ringers Solution (Baxter Healthcare Pty, Old Toongabbie, NSW, Australia) at 4ml/kg/hour was started. The dog was considered suitable for emesis which was induced with apomorphine 0.03mg/kg IV (Apomorphine Hydrochloride, Jurox, Rutherford, NSW, Australia). Care must be taken when inducing emesis in animals poisoned with compounds that affect the central nervous system. Emesis may induce seizures, and compromised animals are also at risk of the inhalation of vomitus. The vomitus contained white creamy material and a dark lichen-like material. The owner had by now identified a container of mouldy Philadelphia Cream Cheese the dog had been eating with mould of the same appearance as the material in the vomitus. Intravenous diazepam (Pamlin; Parnell Technologies NZ Pty Ltd, Auckland NZ) at 1mg/kg only resulted in transient improvement in clinical signs so heavy sedation was induced with pentobarbital (Nembutal; Virbac Laboratories (NZ) Ltd, Auckland, NZ) at 3-15mg/kg slowly IV to effect. As the level of sedation lightened the tremors recurred and so effective sedation was maintained with a constant rate infusion of pentobarbitone at 2mg/kg/hour. A nasal oxygen catheter was introduced and oxygen supplemented at 250mls/min and the dog wrapped in a rug and placed on a warmed floor. Reducing the depth of sedation after six hours resulted in resumption of tremor so the infusion was maintained for 21 hours. Heart rate, respiration rate, temperature, oxygen saturation and blood pressure were monitored but remained within an acceptable range. Recovery from the heavy sedation after 21 hours was uneventful with no resumption of clinical signs. The dog returned home six hours later.

The clinical signs were typical of those reported in other cases of tremorgenic mycotoxicosis. Signs reported in the literature include vomiting, hypersalivation, mydriasis, tachycardia, anxiety, tremor, ataxia and convulsions (Eriksen *et al.* 2010, Hocking *et al.* 1988, Munday *et al.* 2008, Schell 2000, Walter 2002, Young *et al.* 2003.).

The cream cheese was submitted to New Zealand Veterinary Pathology, Hamilton, New Zealand for fungal culture and mycotoxin identification. A definitive diagnosis is established by the identification of the mycotoxins penitrem A or roquefortine in stomach contents but this test is unavailable in New Zealand veterinary diagnostic laboratories. Culture identified *Penicillium* fungi present in the cheese. The identification of *Penicillium* fungi in the cheese, the presence of the cheese in the dog's stomach contents, the clinical findings typical of other reported cases and response to therapy are all support the presumptive diagnosis of tremorgenic mycotoxicosis.

Toxicity

The two most important toxins in naturally occurring disease are penitrem A and roquefortine, both produced by *Penicillium* fungi. These fungi are common contaminants of decaying organic matter (Puschner 2002). Poisoning has been associated with ingestion of a wide range of materials including compost (Boysen *et al.* 2002), general garbage (Walter 2002), mouldy cream cheese(Young *et al.* 2003), rice(Puschner 2002), walnuts (Munday *et al.* 2008), bread (Hocking *et al.* 1988) and pasta (Young *et al.* 2003).

The most toxic of the *Penicillium* tremorgenic mycotoxins is penitrem A. A dose of 0.5mg/kg given to dogs intraperitoneally resulted in the acute onset of tremor leading to death. The injection of 0.125mg/kg resulted in tremor but dogs completely recovered. Oral exposure of 0.175mg/kg resulted in severe muscle tremors in dogs. There are less reports of roquefortine in the literature but the toxin is associated with blue cheeses. The toxins are readily absorbed from the gastrointestinal tract and excreted primarily through the bile. Enterohepatic recycling may occur and contribute to the prolonged recovery (Puschner 2002). While in many cases affected animals including the case study dog make a rapid and complete recovery, reports indicate that in severe cases complete resolution may take months and possibly result in permanent ataxia (Erikson *et al.*).

Conclusion

The lack of published information, pathognomonic clinical signs and laboratory tests makes definitive diagnosis of tremorgenic mycotoxicosis difficult in New Zealand. The free-ranging lifestyles of many rural New Zealand dogs allow frequent access to mouldy organic matter and garbage. They are therefore at risk of Tremorgenic Mycotoxicosis and the incidence of this disease may be significantly underestimated. The disease should be considered in the differential diagnosis of the peracute onset of tremor and ataxia in New Zealand dogs. The Animal Health Diagnostic Laboratory at Michigan State University runs a tremorgen screen including penitrem A and roquefortine as well as strychnine and metaldehyde (Schell 2000).

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A case of canine poisoning with New Zealand tree nettle (Ongaonga, Urtica ferox)

Introduction

The New Zealand Tree Nettle *Urtica ferox* is known to contain the toxic elements histamine, acetylcholine and 5-hydroxytryptamine or serotonin (Blackman and Sumich 1966). Several non-peer reviewed reports describe the clinical signs observed in people following cutaneous contact which include local discomfort, visual disturbances, respiratory distress, neuromuscular signs, collapse and death (Connor 1977, Clark 1993, McGouran 2010). Anecdotal reports of severe cases in dogs describe intense pain, loss of scenting ability, convulsions and death. Deaths have also been reported in horses (Connor 1977). There is widespread anecdotal awareness but published reports of poisonings and treatment protocols are scarce in the human literature (McGouran 2010) and rare in the veterinary literature.

This is a report of *Urtica ferox* poisoning in a dog, including the clinical presentation, comparative human reports, toxicology and treatment discussion.

Case history

A 2-year old 20kg mixed breed pig hunting dog was exposed to significant contact to *Urtica ferox* for a period of 10-20 minutes. The owner reported that approximately 30 minutes after contact the dog became disorientated, staggered and rapidly became recumbent. Two hours following initial nettle contact the dog was presented to a local emergency veterinary clinic where it was reported to be in lateral recumbency, tetraplegic and hypersalivating but with normal vital signs. No dermal signs were evident.

Initial treatment included washing, and medication with 2.5mg/kg mepyramine maleate (Antimine; Ethical Agents Ltd, Auckland NZ) by subcutaneous (SC) injection, 1.5mg/kg dexamethasone sodium phosphate (Dexadresin; Intervet, Auckland, NZ) by intravenous (I/V)injection, 0.05mg/kg atropine (Phoenix Atropine Injection; PhoenixPharm, Auckland, NZ) by S/C injection and 0.015mg/kg buprenorphine (Temgesic; Reckitt Benckiser, Auckland, NZ) by S/C injection.

Following a further three hours of transportation, the dog was presented to the owner's regular veterinary practice. There was little change from first presentation. The dog was in lateral recumbency and unable to stand. Cranial nerve function and mentation were normal. Heart rate, respiratory rate, temperature, mucous membrane colour and capillary refill time were all within normal limits. The dog was able to eat. There was tremor and fine fasciculations of the muscles of the trunk and limbs. Routine haematology, biochemistry and

urinalysis indicated a mild thrombocytopenia of $182x10^9$/l (ref range 200-500), an elevation in creatinine kinase of 1798iu (ref range 0-609) and a positive test for urinary erythrocytes/haemoglobin/myoglobin (Multistix SG10; Siemens).

A single dose of 0.5mg/kg diazepam (Pamlin; Parnell Technologies NZ Pty Ltd, Auckland NZ) by slow I/V injection was given which produced a transient improvement in tremor.

An I/V infusion of compound sodium lactate (Baxter Healthcare Pty Ltd, Old Toongabbie, NSW, Australia) was begun at 10ml/kg/hr for one hour then reduced to 4ml/kg/hr overnight.

The clinical signs slowly abated. Ten hours following presentation the dog was able to stand with assistance, was eating and drinking but still had fine muscle fasciculation. Improvement was continuous but the owner reported it took 10-14 days for the dog to return to total apparent normality.

Discussion

Urtica ferox is native to New Zealand and commonly found in coastal to lowland forest margins and shrubland of the North and South Islands (Allan 1982). The foliage is covered with fine hairs or trichomes which are hollow with a tapered point, and which break after piercing the skin injecting fluid into the tissue (Kankazi *et al.* 2010). This fluid has been shown to carry histamine, acetylcholine and 5-hydroxytryptamine (Blackman and Sumich 1966).

Unsubstantiated reports of clinical signs described in people are similar to the case study dog and include local discomfort and paraesthesia, chills, incoordination, sluggish papillary reflexes, visual disturbances, blindness, hyper-salivation, abdominal cramping, generalised weakness, muscle fasciculation, ataxia and collapse (Connor 1977, Clark 1993, McGouran 2010). One case showed significant rhabdomyolysis (McGouran 2010). In another report, a 21 year old male developed an acute, mainly motor polyneuropathy with two companions similarly but less severely affected. In this case, recovery occurred over a few weeks (Hammond-Tooke *et al.* 2007). There is also an unsubstantiated report of a fatality occurring within five hours of a young adult male stumbling into a patch of Ongaonga in the Ruahine Ranges (Connor 1977).

Initial contact is reportedly followed by local discomfort and pain (Kankazi M *et al.* 2010). Studies with *Urtica thunbergiana* identified oxalic acid and tartaric acid as major persistent pain-inducing toxins (Fu *et al.* 2006) though the amount of these acids present in the sting of *Urtica ferox* is unknown. Studies in rats report moderate pain response with injection of serotonin but could not demonstrate a pain response to either histamine or acetyl choline (Fu *et al.* 2006).

The neuromuscular signs following exposure to *Urtica ferox* have several possible explanations. Serotonin toxicosis can produce similar signs as reported in the study of 21 dogs with excessive serotonin as a result of 5-hydroxytryptophan toxicity. The neuromuscular signs included seizure (nine dogs), depression (six), tremor (five), hyperaesthesia (five), ataxia or paresis (four), disorientation (two), coma (one) and hyperreflexia(one). Four had mydriasis and three had transient signs of blindness. Twelve showed gastrointestinal signs and three affected dogs died. These signs are consistent with those seen in human patients with serotonin syndrome (Gwaltney-Brant *et al.* 2000*)*. Acetylcholine toxicity could also contribute to the neuromuscular signs. Acetylcholine has effects mimicked by both muscarine and nicotine. The nicotinic effects of acetylcholine excess include tremor and neuromuscular signs. There is also evidence to suggest the involvement of a further unidentified neurotoxin. Nerve conduction studies on a person who developed a predominantly motor polyneuropathy following contact with *Urtica ferox* demonstrated markedly reduced compound muscle action potentials and prolonged distal motor latencies and they concluded the stinging hairs contain an unidentified neurotoxin (Hammond-Tooke *et al.* 2007). Fluid from *Urtica ferox* injected into the epineurium of rat sciatic nerves produced a transient axonopathy resulting in paresis by 14 days and recovery by 28 days. Toxin injected nerves at days five and 14 showed a reduction in the number of myelinated fibres. The identity of the toxin remains uncertain (Kankazi *et al. 2010)*. The effect of this toxin may explain the delayed recovery seen in the case study and human patients (Hammond-Tooke *et al.* 2007).

Treatment should initially be directed at decontamination of toxins by bathing while ensuring adequate protection for handlers. Further treatment should be determined by the severity of the clinical presentation and clinical judgment of the veterinarian.

While mild myopathy may have occurred in the case study dog, a human affected by *Urtica ferox* poisoning was reported to suffer significant rhabdomyolysis, considered a result of severe muscle fasciculation (McGouran

2010). The potential for such fasciculations to cause a myopathy and consequent myoglobinuria would indicate that treatment to prevent the precipitation of myoglobin in the renal tubules and acute renal disease may be beneficial. Any fluid deficits should be rapidly corrected and diuresis initiated with the administration of I/V isotonic fluids at 2-3 times maintenance rates. Urine output, specific gravity and renal function should be monitored and urine assessed for the presence of myoglobin by centrifugation and urinalysis. Small amounts of myoblobin in centrifuged urine test positive for blood on urine dipsticks and significant amounts give urine a brown colour in comparison with the red of haemoglobin.

The use of specific antidotes should be considered on a case by case basis. Although the case study dog did not show dermal erythema or wheal typical of exposure to histamine, the presence of histamine in the sting would suggest the use of antihistamines in treatment protocols may be of benefit.

Dogs affected with *Urtica ferox* toxicity exhibit many neuromuscular and gastrointestinal tract signs in common with seratonin toxicity (Gwaltney-Brant *et al.* 2000). Serotonin also has potent platelet aggregating activity and alterations in haemostasis might be expected with serotonin excess (Gwaltney-Brant *et al.* 2000).The case study dog exhibited mild thrombocytopenia. Serotonin syndrome in dogs has been successfully treated with cyproheptadine, a drug with both antihistamine and serotonin antagonistic effects. The recommended dose is 1.1mg/kg per os or per rectum every 1 to 4 hours until signs subside. If little or no effect is seen after the first few doses the drug should be discontinued (Gwaltney-Brant *et al.* 2002). Ongoing monitoring of buccal mucosal bleeding time and platelet numbers are indicated.

Should clinical signs attributable to the muscarinic effects of acetyl choline including bradycardia, hypersalivation and abdominal pain be significant the therapeutic use of atropine at 0.02-0.04mg/kg by I/V injection should be considered (Cote 2001). Atropine will not reverse the nicotinic effects of acetyl choline however.

The administration of 0.5mg/kg I/V diazepam in the case study dog only resulted in transitory improvement. If tremor is severe diazepam at doses used for seizure control of 0.5-1mg/kg slowly I/V repeated every 10 minutes if there is no response up to a maximum of three doses should be considered (Ramsey 2008). The drug must be injected slowly to avoid potential thrombophlebitis and propylene glycol cardiotoxicity, and used cautiously in patients with hepatic or renal disease and in debilitated and geriatric patients (Plumb DC 2002). If diazepam is ineffective in more severe cases heavy sedation with 3-15mg/kg pentobarbital by slow I/V injection to effect and maintenance with a constant rate infusion of 2-4mg/kg/hr should be considered. Use cautiously in patients with hypovolaemia, anaemia, cardiac disease, respiratory disease or depression, renal and hepatic disease (Plumb 2002).

Parameters that need ongoing monitoring and management include body temperature, heart rate, blood pressure, respiratory rate, oxygen saturation, seizure activity, urine output and renal function, myoglobinuria, serum creatinine kinase and platelet counts.

Conclusion

While awareness of *Urtica ferox* toxicity is limited, the consequences to people and animals frequenting New Zealand bush are potentially serious. Clinicians need to recognize the neuromuscular signs associated with toxicity, as they are not typical of cutaneous contact with other nettle varieties. Although some hunters carry prophylactic antihistamines it is unlikely they alone will effectively manage the effects of significant contact.

Treatment protocols should include decontamination by washing and I/V fluid therapy. Antihistamine, serotonin antagonist, atropine and corticosteroid medication should be considered based on the clinical signs. Vital signs should be monitored and maintained. If neuromuscular signs are present, benzodiazepines and pentobarbital should be considered. While significant contact can be fatal, it seems many cases recover. The above mentioned dog in the case report and human reports indicate full recovery may take up to 14 days (Hammond-Tooke *et al.* 2007) although experimental models indicate recovery from an unidentified neurotoxin may take 28 days (Kankazi *et al.* 2010). To enable targeted treatment further study is necessary to identify all the toxic compounds present in *Urtica ferox* and their contribution to the clinical signs following significant exposure.

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