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Mycotoxicity in dogs

- Aflatoxins and tremorgens (penitrem A and roquefortine)

Mycotoxicos (MT) är en potentiellt livshotande förgiftning som orsakar symtom som trötthet, anorexi, ikterus, blödningsrubbningar och diarré hos hund över hela världen efter intag av mykotoxin-förorenad mat eller foder. De mest relevanta mykotoxiner som påverkar hundar är aflatoxiner (AF) och tremorgener (TG) (penitrem A och roquefortine). Denna artikel utgör det skriftliga arbetet av författarens specialistutbildning i hundens och kattens sjukdomar.

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Abstract
Mycotoxicosis (MT) is a possibly life-threatening toxicity. It is rare in humans, but is suggested to be more prevalent in dogs. MT can occur worldwide after ingesting mycotoxin-contaminated food or feed. The most relevant mycotoxins (MS) affecting dogs are aflatoxins (AF) and tremorgens (TG) (penitrem A and roquefortine).

AF are mainly produced by the fungi *Aspergillus flavum* and *Aspergillus parasiticus*, which are common soil contaminants. Dogs are highly susceptible to the effects of AF. They are readily absorbed from the gastrointestinal (GI) tract, mainly sequestered into the liver and excreted via feces and urine. AF are hepatotoxic and can be immunosuppressive and/or carcinogenic. The main clinical signs of intoxication include lethargy, anorexia, icterus, hemorrhagic diathesis and diarrhea. Common laboratory changes include hypoproteinemia, increased serum liver enzymes, hyperbilirubinemia, hypocholesterolemia, coagulopathic and electrolyte disturbances. Detecting AF (or their metabolites) in serum, urine, feed or liver specimens confirms the diagnosis. Treatment focuses on eliminating toxins, hemostatic stabilization and hepatic protection. The prognosis is guarded to poor if the damage involves a large part of the liver.

The main source of TG is the fungus *Penicillium crustosum.* TG are usually formed during food spoilage and are easily absorbed from the GI tract. Toxicity presents as an acute onset of neurological symptoms. The exact mechanism of action and method of excretion is unknown. Hematologic changes are non-specific. Diagnosis is confirmed by identifying TG in blood, urine or allegedly contaminated material. Treatment focuses on controlling tremors and seizures, decontamination and stabilizing the patient. Prognosis is considered to be good if elimination of toxins is performed early.

Introduction

MS are defined as toxic secondary fungal metabolites that poison other organisms (6). They are found to contaminate agricultural commodities worldwide (41). Temperature and humidity affect the types and amounts produced. MS can arise preharvest, at harvest or postharvest (23). The most common route of entry is ingestion of mold-contaminated foods and feeds (6). The main source of MS in the food chain is grains (41). MT is a rare type of intoxication in humans (32, 50). It is suggested that dogs have an increased risk for MT when compared to other animal species, probably due to their scavaging nature (4). The fact that cereal grains are frequently used as ingredients in commercial pet food (28) further supports this theory. The most common MS related to natural outbreaks in dogs are AF and TG (28, 43). Several outbreaks are reported in the last two decades (2, 9, 11, 15, 17, 19, 34, 35, 40, 53, 54, 59, 60). The goal of this literature study is to gather information available on intoxication with AF or TG in dogs. An attempt is made to gather information that helps veterinarians diagnose the toxicities early, minimize exposure and provide adequate treatment so that the best prognosis can be achieved.


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Aflatoxins

Etiology

AF are a group of MS that are mainly produced by the fungi *A flavum* and *A parasiticus* (31, 36). These fungi are found to be common soil contaminants (57). There are four major types of AF: B1, B2, G1 and G2 (37). The most potent, prevalent and pathogenic type is aflatoxin B1 (AFB1) (37, 43). According to the European Union´s *Commission Regulation (EC) No 1881/2006 of 19 December 2006* the maximum allowed limit of AFB1 is 8 µg/kg. This applies to groundnuts intended for human consumption or as an ingredient in foodstuffs.

Aflatoxin-related fatalities in dogs have been linked with contaminated commercial feed (11, 26, 40, 49), corn products (59)

or ingestion of moldy bread (53). Previous studies have generally shown low concentrations of AF in commercial dog food (28). The majority of positive samples contained <20 µg/kg of AFB1 (28, 30, 47). Nevertheless, AF are the most frequent cause of acute MT linked to commercial dog food with maize products as the typical source (8). An outbreak in South Africa 2011 is estimated to have killed over 220 dogs (2) due to ingestion of commercial pet food mostly contaminated with AF. However, a multi-mycotoxin etiology could not be excluded (33).

Toxicity, metabolism and mechanism of action

AF are liposoluble, readily absorbed from the GI tract and mainly sequestered into the liver (1). To exert its toxic effects, AFB1 needs to be transformed to its reactive epoxide: AFB1 8,9 epoxide. This is performed in the tissues of the affected patient by the action of mixed function mono-oxygenase enzyme systems (cytochrome P450-dependent). AFB1 8,9 epoxide is very reactive and may bind covalently to intracellular macromolecules such as DNA, RNA and protein, resulting in adduct formation and cellular damage (16, 25, 31). The main detoxification reaction of AFB1 is conjugation of the reactive epoxide to glutathione, mediated by glutathione S-transferase (GST) (14). Different species have varying susceptibility to AF. Dogs are considered highly susceptible (37). This is partly due to their inherent relatively lower hepatocellular glutathione levels (12, 52), their individual variation in GST activity (55) and the fact that AF are hepatotoxic in dogs. The reported oral median lethal dose (LD_{50}) of AFB1 in dogs is 0.5-1.0 mg/kg of body weight (39).

Previous studies have shown that AF have carcinogenic (38) and immunosuppressive (48) properties in multiple animal species. It has been suggested that studies on aflatoxicosis (AT) in dogs are generally not long enough to show that AF have carcinogenic potential (5). One study on the development of mammary tumors and chronic aflatoxin exposure suggested that AF have carcinogenic properties in dogs (21). It has been shown that the species specificity in toxicity and carcinogenicity also applies to immune responses (56). Clinical signs of hemorrhagic diathesis have occurred in many previous studies on AT in dogs (2, 5, 11, 13, 15, 19, 22, 26, 39, 43, 49, 53, 59). One study did not find the effect of AFB1 on anticoagulant activities in dogs (3) to be statistically significant.

AT is classified as acute, sub-acute or chronic (22, 37). The most commonly reported forms in dogs are acute and sub-acute (13, 22, 40). Elimination of AF occurs via feces and urine (16). AFB1 is cleared from urine within 48 hours after ingestion of aflatoxin (7).

Clinical signs

The main clinical signs of AT in dogs are related to hepatopathy (40, 43). The most common clinical signs include lethargy, anorexia, icterus, hemorrhagic diathesis and diarrhea (2, 5, 11, 13, 19, 26, 39, 43, 49, 53, 59). Common complications of AT include disseminated intravascular coagulation, hepatic encephalopathy and acute renal injury (11). Dogs that present without symptoms may later develop clinical signs that result in mortality (11, 49).

Diagnostic approach

AT is associated with non-specific clinical signs. Therefore, it is mostly diagnosed post mortem (11). Common laboratory abnormalities include hypoproteinemia, increased serum liver enzymes, hyperbilirubinemia, hypocholesterolemia, coagulopathic and electrolyte disturbances (11, 15, 19). Histological examination of liver samples can help confirm the diagnosis or rule out other etiologies (43, 49). Sub-acute and chronic cases of AT typically show bile duct proliferation, fibrosis, hepatocellular fatty degeneration and megalocytosis. Acute cases show massive fatty degeneration and centrilobular necrosis of the liver as well as extensive bleeding (5, 15, 19, 40, 43, 59). To reach a diagnosis of AT, enzyme-linked immunosorbent assay (ELISA), high-performance liquid chromatography (HPLC) and liquid chromatography-tandem mass spectrometry methods (15) are used to identify AF or their metabolites in urine (7, 49), serum, feed or liver specimens (40, 43, 49).

Treatment

No antidote is available and therefore treatment is symptomatic (43). The goals of treatment include elimination of AF, hemostatic stabilization and hepatic protection (11). There is no gold standard for treating AT and previous studies show variation in therapy. Most authors included intravenous (IV) fluids, electrolyte supplements, blood-component treatments, anti-emetics, gastroenteric-protectants, vitamins (K1 and E), thiol donors (IV administration of n-acetylcysteine or S-adenosylmethionine (SAMe) per os (PO)) and antibiotics (11, 15, 49). IV fluids are crucial for correction of hypovolemia plus they facilitate renal elimination of AF (7). One study in 2013 (53) suggested that a tetrasulphate solution (TS) (ferrous-, copper-, zinc- and magnesium sulphate) might reverse the adverse effects of MS and might increase the survival rate in dogs with AT.

Prognosis

Toxicity is correlated to the dose ingested. It has been suggested that small repeated doses are less lethal than a single larger dose (39). The prognosis is estimated as guarded to poor if the damage involves a large part of the liver (43). Mortality rates are most often found to be >63% (2, 11, 26, 40, 49, 59). However, an accidental outbreak in Turkey showed a 70% survival rate (53).

Tremorgens (penitrem A and roquefortine)

Etiology

Over twenty different MS have demonstrated tremorgenic potential (20). The most common tremorgenic MS in dogs are penitrem A and roquefortine (9, 17, 24, 29, 35, 42, 44, 45, 54, 60). For simplification, when TG are mentioned in this paper the author is referring exclusively to penitrem A and roquefortine.

TG are rarely found in feed ingredients but are usually formed during food spoilage (28). Their most common source is the fungus *P crustosum* (58). Tremorgenic mycotoxicity (TM) in dogs has been found to be associated with ingestion of a variety of moldy food or feed (17, 24, 34, 35, 44, 60), overripe blue cheese (42) and old compost (9, 54).

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Toxicity, metabolism and mechanism of action

TG are easily absorbed from the GI tract. They are lipophilic and have the possibility of crossing the blood-brain barrier to enter the central nervous system (CNS) (17). A predominant biliary excretion is suggested (20). Dysfunctional GABA:ergic neurotransmission (18, 27) and inhibition of the high-conductance Ca^{2+} activated potassium channels are believed to be involved in producing the neurotoxic effects (18). The systemic clearance (18), exact mechanism of action and LD_{50} are unknown in dogs (4, 27).

Clinical signs

TM in dogs usually presents as an acute onset of neurological symptoms (such as ataxia, opistotonus, nystagmus, mydriasis, tremors and convulsions (9, 17, 24, 29, 34, 35, 42, 45, 54, 60)). Other possible symptoms include increased salivation, excessive panting, hyperthermia, vomiting, diarrhea, flatulence, tachycardia, recumbency or status epilepticus (9, 17, 60).

Diagnostic approach

In most cases it is hard to differ TM from other neurological diseases that result in tremors. Hematologic values may be altered but are found to be non-specific (17). If blood samples are normal and tremors are the only neurological symptom, a primary neurological disorder or toxin ingestion are suggested to be more likely than a secondary disorder (4). A poor response to diazepam anticonvulsive therapy has been suggested to indicate TM rather than other neurologic toxicities (29). However, most recent studies show conflicting results on the effects of diazepam against TG related convulsions (9, 17). Diagnosis is confirmed by identifying TG (by thin-layer chromatography (TLC), HPLC and/or mass spectrometry techniques) in stomach contents, vomited material, blood, urine or allegedly contaminated material (10, 51).

Treatment

No antitoxin is available, therefore treatment is symptomatic. If the patient presents with seizures at arrival, initial care should focus on anticonvulsive therapy. The standard treatment for persistent seizures is IV anticonvulsants such as diazepam, midazolam, phenobarbital and levetiracetam. If there is no response to initial anticonvulsive therapy, general anaesthesia can be induced (4). The use of propofol, ketamine or inhalation anaesthesia is suggested (4). Rarely, intubation for oxygen support may be necessary due to respiratory distress (9).

Once seizures are managed or nonexistent, muscle relaxants (e.g. methocarbamol) or sedatives (e.g. medetomidine) can be administered to reduce or control tremors (4, 46). Thereafter, the main focus of treatment is minimizing absorption of toxin from the GI tract. In asymptomatic patients that present 15-30 minutes after suspected or confirmed intoxication, this can theoretically be done by induction of emesis (4). Administration of activated charcoal (PO or via stomach tube) and motility stimulants (e.g. sorbitol given rectally) may decrease absorption of toxin from the GI tract (4, 43, 46).

When there is suspicion of massive ingestion, vomiting has not occurred or the patient is symptomatic, gastric lavage (GL) is strongly recommended. Generally, GL requires anesthesia and intubation (43). Careful monitoring of respiration is advised, as aspiration-pneumonia is one of the most common complications to decontamination treatment (9, 29). Thermoregulation should be performed when necessary along with careful monitoring, as animals often initially present with hyperthermia but quickly become hypothermic secondary to initiated therapy (9).

Prognosis

If decontamination is initiated early, prognosis is generally considered to be good (43). Most dogs make a full recovery within 48 hours from initiating treatment (9, 17, 24, 29, 34, 35, 42, 45, 54, 60). However, one study reported of an English setter who still presented as ataxic and unable to walk up stairs three years after exposure to *P crustosum* (17). When the stomach is not emptied prognosis depends on the amount of TG ingested, but should generally be estimated as guarded (43).

Discussion

Aflatoxins

An interesting subject for future studies is why AF are the most frequent cause of acute MT linked to commercial dog food, even if the AF levels in the food are generally found to be low (28). Possibly a multitoxin-etiology has been overlooked, as was suggested in the South African outbreak in 2011 (33), or perhaps synergistic effects are to blame.

The hepatotoxicity of AF in dogs has long been established (39), but whether they are immunosuppressive, carcinogenic and/or induce coagulopathies is unclear. Further studies on the subject are needed to conclude on the matter.

A suspected exposure to AF should not be taken lightly, as previous studies have reported of dogs dying that initially presented without symptoms (11, 49).

None of the previous studies discusses treatment with emetics, activated charcoal or GL as options in eliminating AF. Whether this is because most dogs presented with vomiting at admission (15, 19) or other factors is unknown. The author sees no reason why these treatments should not be used for decontamination if the patient does not present with vomiting and is stable enough for general anaesthesia to perform GL. Interestingly only one study used lactulose as a hepatic protectant (11). It can be questioned whether antibiotics are needed as a part of the treatment against AT.

No study was identified stating the time it takes to metabolize AFB1 to AFB1 8,9 epoxide. As the toxic effects are performed by the epoxide, this could explain why none of the authors in previous studies discusses timing of decontamination as a factor in evaluating prognosis. It can be hard to evaluate prognosis, as it depends on the severity and extent of hepatic dysfunction (43).

Most studies found mortality rates to be >63% which suggests a guarded to poor prognosis (2, 11, 26, 40, 49, 59). Recently a study on Rottweilers with AT suggested that a TS could be used as an antidote against AT (53) and that a survival rate of 70% could be achieved. As this study only included ten dogs of one specific breed, it is not possible to conclude whether or not TS can be used as an antidote in dogs with AT. Whether the high survival rate was due to breed specificity, duration of exposure (several weeks), toxin dosage, differences in therapy or other factors is impossible to conclude on. Further studies on the subject are indicated as these results give hope that an antidote might be found and a higher survival rate can be achieved.

Tremorgens (penitrem A and roquefortine)

In contrast to AF, there seems to be no legal limit for TG in food and no reported outbreak involving more than ten dogs. This might be due to the fact that TG are rarely found in feed

ingredient and usually form during food spoilage (28), making it hard to create as large exposure as is often the case with AF.

Unfortunately, a lot is still unknown about TG. Further studies are needed to be able to conclude on the method of systemic clearance, the LD_{50} and the exact mechanism of action.

None of the dogs in previous studies presented as asymptomatic (9, 17, 24, 29, 34, 35, 42, 45, 54, 60). Therefore, the relevance of administration of emetics in asymptomatic patients that present early is questioned.

Lipid emulsion treatments are generally gaining acceptance as possible treatments for lipophilic drug toxicity. As AF and TG are lipophilic, an interesting subject for future studies is the effect of intralipid treatment against these toxicites. Unfortunately, none of the previous studies discusses intralipid treatment as a possibility.

When genereal anaesthesia is necessary to control convulsions, propofol and/or inhalation anaesthetics probably are better options than ketamine, as ketamine can increase the intracranial pressure.

FOTO: NINNI ZACKRISSON

Mykotoxiner eller mögelgifter kan utgöra en fara för hundar och andra djur.

The fact that prognosis not only depends on whether gastric emptying is performed but also timing of decontamination (43), underlines the importance of performing GL in all patients that have not vomited and massive ingestion is suspected.

Although, the majority of dogs make a full recovery within 48 hours (9, 17, 24, 29, 34, 35, 42, 45, 54, 60) it must be remembered that recovery can be prolonged for years after exposure (17).

Conclusion

Aflatoxins

The main sources of AF are the fungi *A flavum* and *A parasiticus,* which are common soil contaminants. There are four major types of AF. The most potent, prevalent and pathologic is AFB1. AF are readily absorbed, mainly sequestered into the liver and excreted via feces and urine. Dogs are highly susceptible to AF, which are hepatotoxic and can be immunosuppressive and/or carcinogenic. Most often dogs present with acute and sub-acute AT. The main clinical signs include lethargy, anorexia, icterus, hemorrhagic diathesis and diarrhea. Common laboratory changes include hypoproteinemia, increased serum liver enzymes, hyperbilirubinemia, hypocholesterolemia, coagulopathic and electrolyte disturbances. Detecting AF or their metabolites in serum, urine, feed or liver specimens confirm the diagnosis. Treatment is symptomatic and focuses on eliminating toxins, hemostatic stabilization and hepatic protection. The prognosis is guarded to poor if the damage involves a large part of the liver.

Tremorgens (penitrem A and roquefortine)

The main source of TG is the fungus *P crustosum*. Usually TG form during food spoilage. They are easily absorbed and have the ability of entering the CNS. The exact mechanism of action and method of excretion is unknown. TM presents as an acute onset of neurological symptoms. Hematologic changes are non-specific. Diagnosis is confirmed by identifying TG in blood, urine or allegedly contaminated material. Treatment is symptomatic and focuses on controlling tremors and seizures, decontamination and stabilizing the patient. Prognosis is generally considered to be good if elimination of toxin is performed early.

Sammanfattning

Mycotoxicos (MT) är en potentiellt livshotande förgiftning, sällsynt hos människor, men menas vara mer utbredd hos hundar. MT kan förkomma över hela världen efter intag av mykotoxin-förorenad mat eller foder. De mest relevanta mykotoxiner som påverkar hundar är aflatoxiner (AF) och tremorgener (TG) (penitrem A och roquefortine).

AF produceras huvudsakligen av svamparna *Aspergillus flavum* och *Aspergillus parasiticus*, som är vanliga kontaminanter i jord. Hundar är mycket mottagliga för AF-påverkan. AF absorberas lätt från mag-tarm (GI)-kanalen, ansamlas huvudsakligen i levern och utsöndras med avföring och urin. AF är hepatotoxiska och kan vara immunosuppressiva och/eller cancerogena hos hundar. De mest vanliga kliniska symtomen på förgiftning är trötthet, anorexi, ikterus, blödningsrubbningar och diarré. Vanliga biokemiska förändringar är hypoproteinemi, förhöjda serumleverenzymer, hyperbilirubinemi, hypokolesterolemi, koagulations och elektrolytstörningar. Diagnosen fastställs vid detektion av AF eller deras metaboliter i serum, urin, foder eller leverprover. Behandlingen fokuserar på att eliminera toxiner, hemostatisk stabilisering och att skydda levern. Prognosen är avvaktande till dålig beroende på hur stor del av levern som påverkats.

Svampen *Penicillium crustosum* är den huvudsakliga källan till TG. TG bildas vanligtvis vid förruttnelse av mat och absorberas lätt från GI-kanalen. Första tecknen på förgiftning är akut uppkomst av neurologiska symtom. Exakt verkningsmekanism och toxinernas utsöndring är okänd. Hematologiska förändringar är ospecifika. Diagnosen fastställs vid förkomst av TG i blod, urin eller i misstänkt förorenat material. Behandlingen fokuserar på att kontrollera tremor och kramper, dekontaminering och stabilisering av patienten. Prognosen anses vara bra om eliminering av toxiner utförs tidigt. •

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FRÅGAN

Vilken är din diagnos?

SVAR SIDA 52

EPIZOOTOLOGI

I fallet som är fiktivt utreds neurologiska symtom hos häst. Fallet presenteras av Elina Åsbjer, SVA.

ANAMNES:
Det är sommar och en veterinär blir utringd till ett större stall där ett par hästar haft en mildare övergående feber. En av dessa hästar hade dagen innan veterinärbesöket upplevts som väldigt stressad, verkat rädd för saker den inte tidigare varit rädd för och även upplevts beröringskänslig. Djurägaren trodde först det berodde på att hästen varit irriterad av alla insekter, men nu hade samma häst även fått muskelryckningar i främst mulen, men även ögonlock och allmäntillståndet var lite nedsatt. Enligt djurägaren verkade hästen även ha någon form av rörelsestörning, och djurägaren upplevde hästen som muskelsvag med lite dålig balans, varpå djurägaren ville att hästen skulle undersökas av veterinär.

FRÅGOR
Vilken eller vilka sjukdomar ska misstänkas och hur ska veterinären gå vidare med fallet? •

Fig. 1: Vilka är dina diffdiagnoser för en häst med neurologiska symtom?