Salivary gland enlargement and sialorrhoea in dogs with spirocercosis: A retrospective and prospective study of 298 cases

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This longitudinal cross-sectional clinical study investigated the incidence of sialorrhoea in dogs with spirocercosis and determined whether breed, body weight and the extent of the oesophageal involvement was associated with this presentation. A retrospective analysis was performed on the medical records of 233 dogs and information pertaining to 65 dogs was collected as part of a prospective study. All the animals were client-owned. Patients from the retrospective study underwent thoracic radiography or oesophageal endoscopy to diagnose and characterise the infection and were placed on therapy with a macrocyclic lactone, whereas the patients in the prospective study had both radiography and endoscopy routinely performed and biopsies of the oesophageal nodules collected where possible. Tru-cut biopsies of affected salivary glands were taken in 10 of 13 patients demonstrating clinical signs of sialorrhoea and salivary gland enlargement. The entire salivary gland was sectioned in an additional three dogs with spirocercosis and no sialorrhoea that were presented for *post mortem* examination. Sialorrhoea was present in 33/298 cases (11%). Fox terrier breeds were over-represented in the patients with sialorrhoea, comprising 36% of cases, whereas they only comprised 1.5% of the patients without sialorrhoea ($p < 0.001$, chi squared test) and 5% of the combined group. Dogs weighing 12 kg or less were significantly over-represented in the sialorrhoea group, 69% *versus* 19.5% ($p < 0.001$, chi square test). Age was not significantly different between the two groups ($p < 0.08$, Mann-Whitney test). The number of oesophageal nodules per case was significantly higher in the non-sialorrhoea cases ($p = 0.048$, Mann-Whitney test). The prevalence of distal oesophageal and lower oesophageal sphincter involvement, and neoplastic transformation of the nodules were not statistically different between the two groups. None of the fox terriers in either group showed neoplastic transformation of the parasitic nodules even though they were over-represented as a breed. Mandibular salivary glands were affected in 86% of cases showing sialorrhoea. Histopathology revealed acinar hyperplasia in all cases with concurrent necrosis detected in only two cases.

Sialorrhoea and salivary gland enlargement has an incidence of 11% (33/298 cases) in canine spirocercosis. Small breeds (≤ 12 kg) and particularly fox terrier breeds are over-represented in the group demonstrating sialorrhoea and this appeared to be the only risk factor.

The conclusion was that sialorrhoea secondary to canine spirocercosis occurs frequently and its presence should prompt further investigation for oesophageal and gastro-intestinal disease. Severely affected patients can be managed with phenobarbitone to control the dysphagia in addition to the routine macrocyclic lactones treatment.

Introduction

Spirocercosis is a worldwide disease caused by the nematode *Spirocerca lupi* and is widespread and common in South Africa (Lobetti 2000). Canidae are the primary definitive host and present with a variety of clinical signs that occur because of larval migration from the stomach to the thoracic aorta, which may take 3–4 months, and because of persistence of the adult worms within the host (Hu & Hoeppli 1936; Van der Merwe *et al*. 2008). A variety of species of coprophagous beetles act as the intermediate host that ingests larvated eggs from canine faeces and allows development to L3 (life cycle stage 3). The L3 utilises a great variety of paratenic hosts, including poultry, wild birds, lizards, rodents, hedgehogs and rabbits (Chabbra & Singh 1972; Fox, Burns & Hawkins 1988). Adult worms are typically found from 3–9 months post-infection, embedded within nodules in the wall of the oesophagus (Bailey 1963; Dvir, Clift & Williams 2010; Sen & Anataraman 1971). The adult nematode is a large spiralled pink worm with male worms of up to 54 mm and female worms of up to 80 mm in length (Taylor, Coop & Wall 2007). Histopathology of non-neoplastic nodules has shown that these nodules consist of variable quantities of fibroblasts and collagen, as well as foci of suppurative and/or lymphoplasmacytic inflammation (Dvir *et al*. 2010).

The typical clinical signs of canine spirocercosis include regurgitation and/or vomiting and weight loss (Mazaki-Tovi *et al*. 2002; Van der Merwe *et al.* 2008). Other frequently encountered clinical signs include coughing, dysphagia, pyrexia, melaena and sialorrhoea (Mazaki-Tovi *et al.* 2002; Schroeder & Berry 1998; Van der Merwe *et al.* 2008). Doramectin (Dectomax, Pfizer AH) is an effective therapy for uncomplicated spirocercosis (Berry 2000; Lavy *et al*. 2002).

Sialorrhoea, ptyalism or hypersialosis are synonyms used to describe the excessive production of saliva. This condition may arise from oral, pharyngeal and oesophageal disorders, central nervous system (CNS) disorders, gastritis, high-protein diets, cholinergic drugs, and toxins such as organophosphates (Boyce & Bakheet 2005; Brooks, Hottinger & Dunstan 1995; Pandol & Isenberg 1990). Salivation is normally stimulated by olfaction, taste, chewing and dryness of the oral, pharyngeal or oesophageal mucosa (DeBowes 2010; Guyton 1997). Salivation can also be stimulated through the oesophago-salivary reflex, where afferent neural impulses originating from the oesophagus act directly on the salivary nuclei, increasing salivary flow (Boyce & Bakheet 2005; Kay & Phillipson 1959; Sarosiek *et al*. 1994). Innervation of the oesophagus is via the vagal and splanchnic nerves. Sensory vagal afferent fibres are thought to be low-threshold mechanoreceptors which are stimulated by oesophageal distension and mechanical obstruction (Sarosiek *et al.* 1994; Spangler & Culbertson 1991). Stimulation of these fibres results in increased salivation, reportedly up to 15 x basal rates in sheep and up to 9 x basal rates in human beings with mechanical oesophageal obstruction (Kongara & Soffer 1999). Central stimulation results in activation of the cholinergic pathways through the salivary nuclei (Boyce & Bakheet 2005; Kay & Phillipson 1959; Sarosiek *et al.* 1994).

Salivary gland enlargement is an uncommon condition in dogs (Spangler & Culbertson 1991). In a review of 245 salivary gland biopsies from animals, salivary glands accounted for only 0.3% of all biopsies received (Spangler & Culbertson 1991). The majority of these biopsies (65%) were obtained from dogs and demonstrated neoplasia (30%), inflammation (29%), sialocoele formation (11%), infarction (9%), with the remainder showing miscellaneous changes (Spangler & Culbertson 1991). The nomenclature for bilateral salivary gland enlargement is confusing and is variably referred to as, (1) sialoadenosis, a uniform hypertrophy and hyperplasia of the functional acini, (2) necrotising sialometaplasia, a diffuse coagulative necrosis with inflammation and salivary gland infarction and (3) coagulative necrosis of acinar tissue (Boydell *et al*. 2000a; Boydell, Pike & Crossley 2000b; Brooks *et al.* 1995; Harvey 1981; Mawby *et al*. 1991; Schroeder & Berry 1998). All the conditions described by these terms, despite variations in histological descriptions, cause similar clinical signs of retching, gulping, anorexia, nausea, vomiting and sialorrhoea with firm palpable, often enlarged salivary glands, and the majority of publications are about affected dogs with only one reference to an affected cat (Boydell *et al.* 2000b; Chapman & Malik 1992; Schroeder & Berry 1998; Stonehewer *et al*. 2000).

Underlying diseases of the oesophagus and stomach such as spirocercosis, reflux oesophagitis and gastritis, have been shown to cause sialonecrosis and dysphagia (Schroeder & Berry 1998). In some published cases no underlying cause was found and limbic epilepsy or idiopathic hypersialosis was the final diagnosis (Chapman & Malik 1992; Stonehewer *et al.* 2000). The fox terrier breed has demonstrated a predisposition to the idiopathic form of this condition as the breed predominates in most of the literature published (Boydell *et al.* 2000a; Brooks *et al.* 1995; Cooke & Guilford 1992; Harvey 1981; Kelly *et al*. 1979). A rapid clinical response, within 48 hours, to phenobarbitone treatment at 2 mg/kg twice daily (*bid*) has been reported, supporting a nervous system and possible vagal overstimulation as a cause for this presentation (Boydell *et al* 2000a; Brookes *et al.* 1995; Chapman & Malik 1992).

The diagnosis of spirocercosis was made in all cases by a combination of thoracic radiographs where the typical findings of a caudodorsal oesophageal mass with either spondylitis or aortic undulation were used as diagnostic criteria, as well as positive faecal floatation and the presence of one or more nodules identified during oesophageal endoscopy. Neoplastic transformation of the *S. lupi* induced nodule was confirmed by endoscopically collected biopsies and/or *post mortem* samples.

At the Onderstepoort Veterinary Academic Hospital (OVAH), salivary gland enlargement with profound clinical signs of pharyngeal dysphagia was noted in some cases of spirocercosis and this 'swallowing disorder' was often the main reason for presentation. The aim was thus to determine the incidence of sialorrhoea in canine spirocercosis and to determine whether breed, body weight, the number of nodules, lower oesophageal involvement, and neoplastic transformation predisposed to the development of this complication in this disease. An additional aim was to perform a histopathological examination of salivary gland tissue to determine what, if any, changes were present.

Materials and methods

Patients diagnosed with spirocercosis, as well as showing clinical evidence of sialorrhoea and salivary gland enlargement, were selected from both retrospective and prospective data sets. The retrospective study included the files of all dogs diagnosed with spirocercosis between 2001 and 2005 at the OVAH where the diagnosis was confirmed by either thoracic radiographs or oesophageal endoscopy and where the patients were treated with a macrocyclic lactone, Dectomax® (Pfizer AH) and less frequently Ivermectin® (Merial) for treatment. A total of 233 cases of spirocercosis were identified for analysis, of which 20 cases were cross-referenced to treatment with phenobarbitone.

A prospective study, initiated in 2007 at the OVAH, identified an additional 13 patients from 65 patients enrolled at that time. The prospective study comprised a standardised protocol: clinical examination, blood sample collection and

storage, specific thoracic radiographic views, oesophageal endoscopy, and biopsy of the oesophageal nodule if possible, and salivary glands if enlarged**.** The study was approved by the Ethics Committee of the Faculty of Veterinary Science.

The data from the 20 retrospective cases of sialorrhoea were only included in the analysis for the signalment and prevalence of spirocercosis, as information from these cases was limited and files were incomplete. The patients in the prospective study were divided into two groups: dogs with, and without, salivary gland involvement. The data from these two groups were compared for breed prevalence, age, the presence of concomitant oesophagitis, involvement of the lower oesophageal sphincter (LES), neoplastic transformation of the nodule, the number of oesophageal nodules and body weight. The prevalence of the above-mentioned parameters in the two groups was compared by using the chi-square (χ^2) test with Excel software (Microsoft, Washington, USA). Numeric parameters (the number of oesophageal nodules) were compared by using the Mann-Whitney Test with SPSS Statistics 17.0 software (SPS Inc., Chicago, USA). The level of significance was set for $p \leq 0.05$.

Multiple biopsies were taken by using a 14 G tru-cut biopsy needle, under general anaesthesia from the parotid and/or mandibular salivary glands, from 10 of the 13 dogs in the prospective study. An additional four dogs diagnosed with spirocercosis and presented for necropsy had the entire mandibular salivary gland resected and a number of sections made: one of these cases had a history of salivary gland involvement and three did not. The salivary glands of an additional two dogs that were presented for necropsy without macroscopically obvious salivary gland pathology, any oesophageal disease, or evidence of *S. lupi* infection, were used as normal controls for the histopathology. The sections were stained with haematoxylin and eosin (H&E) for routine histopathology.

Ethical considerations

The danger of unethical practices by the researchers was minimised as all animals were client-owned and presented with a natural infection. All procedures and treatments were conducted according to previously published norms for this condition.

Results

The results are summarised in the following passages. Of the 233 dogs diagnosed with spirocercosis in the retrospective analysis, 20 patients were treated with phenobarbitone specifically for salivary gland enlargement, sialorrhoea and dysphagia, an incidence of 8.5%. In the prospective trial 13 of 65 patients showed sialorrhoea and salivary gland involvement, an incidence of 20%. The combined incidence of sialorrhoea in dogs with spirocercosis from both data sets was calculated at 11% (33/298).

Breeds affected, using data from both studies ($n = 33$), included fox terriers or Jack Russell terriers (12), Staffordshire terriers (5), miniature Doberman pinschers (4), cross-breeds (5), golden cocker spaniels (2), Border collies (2), English bull terrier (1), Labrador (1) and Chihuahua (1). The breed names fox terrier and Jack Russell terrier are often incorrectly applied at OVAH, and thus the two breeds have been combined. The fox terriers and Jack Russell terrier breeds accounted for 36.4% (12/33) of the population of dogs with spirocercosis with sialorrhoea, compared with only 4/265 (1.5%) of the dogs with spirocercosis without sialorrhoea ($p < 0.001$). In addition to breed prevalence, breed size was also correlated to the risk of showing severe sialorrhoea if infected with *S. lupi*. To facilitate the analysis, dogs were defined as being of a smaller breed if they weighed 12 kg or less. Mass was not reliably recorded in the retrospective cases. The median body weight of all cases in the prospective group ($n = 65$) was 21.6 kg (range: 3.4–51.0), the median mass of the subgroup with sialorrhoea ($n = 13$) was 9.8 kg (range: 3.4–26.6), and that of the non-sialorrhoea group ($n = 52$) was 23.9 kg (range: 5.0–51.0). The majority (69%) of dogs in the sialorrhoea group weighed ≤ 12 kg *versus* only 19.5% in the non-sialorrhoea group, which was significant ($p = 0.001$).

An analysis of the clinical history of the sialorrhoea group revealed that the duration of clinical signs ranged from 4 days to 3 months and included regurgitation, intermittent to persistent retching, gulping with repeated swallowing movements, coughing, making efforts to 'clear the throat', apparent choking, excessive salivation and anorexia. Clinical signs worsened with excitement or palpation of the pharyngeal area and glands. The choking episodes could be quite severe with the dogs vocalising, scratching at their faces with their forepaws, contorting the forequarters, head and neck, and these symptoms were even on occasion misinterpreted by owners and referring veterinarians as seizures. Retching often terminated in vomition or regurgitation. Where mentioned, the vomitus was generally described as frothy saliva. A variety of anti-emetics including metoclopramide, betaperamide and chlorpromazine had been used to no avail in the majority of the cases referred. None of the patients in the prospective study had severe periodontal disease. Records were inadequate to evaluate this clinical parameter for the retrospective cases. All patients had weight loss. In the longstanding cases clinical signs generally progressed to severe dysphagia and a disinclination or a reluctance to eat. Food aversion was specifically noted in three cases. Laboured respiration was noted by owners in two cases and was detected on clinical examination as abdominal respiration in 25% of the dogs. The mandibular salivary glands were enlarged in 86.6% of cases and the parotid glands were involved in 13.3%.

In the prospective study additional parameters were evaluated to try and establish a risk factor or predisposing cause for the development of sialorrhoea in the 13 dogs with these clinical signs, compared with the remaining 52 dogs without sialorrhoea. Age was not significantly different between the two groups with a median of 50.9 months (range 10–138) in the non-sialorrhoea group and 48 months (range 9–96) in the sialorrhoea group ($p = 0.95$), and there was a substantial

overlap between the groups. Patients with sialorrhoea had an increased incidence of oesophagitis, 25% compared to 12.5% in the non-sialorrhoea group, but the difference was not statistically significant ($p = 0.260$). The median number of nodules were one (range: 1–5) in the sialorrhoea group *versus* two (range: 0–9) in the non-sialorrhoea group, and the difference was statistically different ($p = 0.048$). Involvement of the extreme distal oesophagus or LES was evident in 3 of the 13 sialorrhoea cases (23%), and in 11 of the 52 non-sialorrhoea cases (22%), which was not statistically different. All cases showed increased amounts of foamy saliva in both the oesophagus and the stomach on endoscopic examination.

Neoplastic transformation occurred in 31% of the sialorrhoea group *versus* 24% of the non-sialorrhoea group and this difference was not significant ($p = 0.550$). Tumour types identified included osteosarcoma (10), fibrosarcoma (3), and anaplastic sarcoma (3).

Salivary gland biopsies collected in 10 of the 13 patients in the sialorrhoea sub-group were evaluated under the light microscope. The most consistent finding was the presence of obvious multifocal and often widespread small clusters (3–5 cells) of acinar epithelial cells at the periphery of acini throughout the sections of glands. Occasional mitoses were observed within these clusters of acinar epithelium. There was also occasional, but obvious, 'piling up' of immature progenitor-like epithelial cells that occurred segmentally within the lining epithelium of striated intra-lobular ducts in particular, and to a lesser extent within the intercalated intra-lobular ducts. There was also evidence of mild to moderate and only occasionally severe periductal fibrosis, sometimes associated with interstitial fibrosis. In most cases there were interstitial accumulations of small lymphocytes and plasma cells. Three cases showed, respectively, collagenolysis that was accompanied by invading neutrophils and mononuclear cells, a single small chronic infarct, and severe acute widespread coagulative necrosis.

Salivary gland sections from all three necropsies of dogs with spirocercosis, but without a history of sialorrhoea, showed histological salivary gland changes similar to those observed in the cases with clinical sialorrhoea. Apart from occasional interstitial accumulations of lymphocytes and plasma cells, histopathology of salivary glands from the control group (dogs without spirocercosis or oesophageal disease) revealed no significant abnormalities.

All patients with hypersialosis were treated with doramectin (Dectomax, Pfizer AH), phenobarbitone (Lethyl, Pharmacare Ltd. SA) and other symptomatic therapies as required. The treatment regimen of doramectin varied amongst clinicians but generally complied with the following: 400 µg/kg *per os* or by subcutaneous injection every week or every second week for a minimum of six treatments or until regression of the nodules occurred. The initiating dosage of phenobarbitone was generally around 2 mg/kg *bid* with a duration of 2–6 weeks as required. A marked decrease in clinical signs was generally noted within 48 hours of initiating phenobarbitone treatment. Three cases took up to 2 weeks to respond and in these cases either an oesophagostomy tube or percutaneous endoscopically placed gastrotomy (PEG) tube was inserted (the tube is surgically placed through the skin and not just pushed down the throat or just inserted). The salivary glands decreased in size and became non-painful to palpate over approximately 2–4 weeks.

Trustworthiness

There is always a degree of subjectivity involved in the interpretation of data collected based on human experience. Some of the data is numerical and can be measured in a simple 'yes/no' manner, for example in the conclusion of observations of nodules, weight and so forth, as opposed to the description of clinical signs which is a subjective process. During the research, the danger of subjectivity was noted and the researchers endeavoured to minimise subjectivity by use of a standardised clinical and history questionnaire and check form.

Discussion

The differentials to consider in cases with sialorrhoea and salivary gland enlargement are any oral and pharyngeal disease, oesophageal disease, peri-oesophageal mediastinal disease, to a lesser extent gastric disease, as well as idiopathic limbic epilepsy or hypersialosis (Boydell *et al*. 2000a; Chapman & Malik 1992; Schroeder & Berry 1998). Drugs may also cause sialorrhoea but this is not a known typical side effect of the anti-emetics used in these patients or of the other drugs they were on, *viz* amoxicillin or, amoxicillin and clavulanic acid. If endoscopic evaluation of the stomach and oesophagus reveals no lesions and there is no histological evidence of gastritis or oesophagitis, a diagnosis of idiopathic phenobarbitone-responsive hypersialosis can be made (Chapman & Malik 1992). Salivary gland enlargement with variable histological descriptions has been reported and may be a secondary reactive change because of over-stimulation by the parasympathetic system (Boydell *et al*. 2000a; Chapman & Malik 1992; Cooke & Guilford 1992; Gibbon, Trapanier & DeLaney 2004). It has been suggested that the idiopathic form of the disease may be a form of epilepsy, namely limbic epilepsy (Stonehewer *et al*. 2000). The terrier breeds, especially fox terriers and Jack Russell terriers, are over-represented in the literature on both secondary and idiopathic sialorrhoea, and the current study showed the same trend in spirocercosis (Boydell *et al* 2000a; Brooks *et al.* 1995; Harvey 1981; Stonehewer *et al.* 2000).

The incidence of sialorrhoea in the retrospective group of patients was 8.5% and 20% in the prospective group. The prospective group was much smaller than the retrospective group which implies that the data could be slightly skewed, but the increased incidence probably indicates that an increased awareness of the condition and more specific questioning lead to an increased clinical recognition of this complication and consequently to improved management.

It is also possible that the number of affected patients was underestimated in the retrospective study as the diagnosis hypersialosis was implied by cross-referenced with phenobarbitone, the treatment, rather than with a clinical sign. If the condition was not recognised and treated it would not have been included, because the record system available for that period was a financial accounting system that allowed for treatments and diagnoses to be searched but not clinical data. The combined prevalence, therefore, of 11%, although probably underestimating the true prevalence of this complication, does indicate that clinically significant sialorrhoea is not uncommon in dogs with spirocercosis.

Dog breeds predisposed to spirocercosis are active outdoor dogs and lifestyle is a major risk factor for infection (Mylonakis *et al*. 2001). Of the 298 cases with spirocercosis evaluated in this study, only 5% were fox terrier breeds whereas they accounted for 36.3% of the sialorrhoea cases and only 1.5% of non-sialorrhoea cases. This is a significant breed predilection. An argument can be made that the spirocercosis was in fact an incidental finding in some cases as a consequence of the breeds' predisposition to idiopathic limbic epilepsy or sialonecrosis, but in the authors' opinion the percentage is too high for it to be mere coincidence (Chapman & Malik 1992; Stonehewer *et al.* 2000). Sialorrhoea was also more prevalent in smaller dogs with 69% of affected animals having ≤ 12 kg body weight. It is hypothesised that this may be caused by a relatively greater degree of oesophageal distension in these smaller animals caused by the parasitic nodule, as it has been demonstrated that the vago-oesophageal reflex can be stimulated by distension (Sarosiek *et al.* 1994). *Spirocerca lupi* parasitic nodules result in local distension of the oesophageal wall and even partial obstruction of the oesophagus in more advanced cases, which may stimulate the low-threshold mechanoreceptors of the vagal afferent system and thus cause the sialorrhoea. These nodules can also result in oesophageal mucosal irritation, inflammation and pain, which would stimulate the splanchnic receptors, resulting in sialorrhoea from higher CNS centres (Kay & Phillipson 1959; Reid & Titchen 1988). Increased amounts of foamy saliva in both the oesophagus and the stomach were found in all 13 prospective sialorrhoea cases, confirming that the increased amount of saliva was a consequence of increased salivation and not the patient's inability to swallow. In the authors' experience this amount of saliva is generally not noted in *S. lupi* infected animals without clinical signs of sialorrhoea.

The number of nodules was statistically different between the groups, with the sialorrhoea group having fewer nodules than the non-sialorrhoea group. This phenomenon cannot be explained but it is theorised that these patients show clinical signs earlier in the disease process because of the hyper-responsiveness of the oesophago-salivary reflex. Neoplastic transformation of oesophageal nodules occurred in 31% of the patients with sialorrhoea and in 24% of those without, and was not significantly different between the groups.

None of the fox terriers in either group showed neoplastic transformation of the parasitic nodule even though they were over-represented as a breed. It could be construed that their predilection for showing sialorrhoea in response to the parasitic oesophageal nodule resulted in earlier diagnosis and treatment of the disease.

Involvement of the extreme distal oesophagus and LES was evaluated as it was theorised that this would promote gastro-oesophageal reflux and oesophagitis, which is a described cause of sialorrhoea, but this parameter was not significantly different between groups (Schroeder & Berry 1998). The oesophagitis that occurred in these patients was very mild. The increased incidence of oesophagitis in the sialorrhoea group was also not significantly different from the non-sialorrhoea group.

The histopathology of the salivary glands was remarkably consistent. Changes included acinar cell immaturity, ductal epithelial hyperplasia, and interlobular and intralobular fibrosis and inflammation. Mild lymphoplasmacytic infiltration in the salivary gland appears to be normal as this was present in two normal dogs, but the degree of infiltration was subjectively considered to be more severe in some of the sections from affected patients (Kelly *et al.* 1979). These mild changes are similar to those reported in a retrospective study of 13 dogs (Boydell *et al.* 2000a). Only 2 of 13 salivary gland samples from the cases studied showed evidence of ischaemic or vascular occlusive pathology. It was an unexpected finding that the three necropsy cases with *S. lupi* without any clinical history of salivary gland involvement showed identical salivary gland histopathology to those of the affected dogs. The hypothesis is that the neural reflex is present in all affected dogs resulting in salivary gland changes, but that clinical signs are only evident in some dogs. The trigger for the presence of clinical signs is at this stage unknown, but breed and size seem to play a role.

All patients with *S. lupi* infection will exhibit a degree of dysphagia and regurgitation. However, the dysphagia exhibited by patients with sialorrhoea can be extreme. The sialorrhoea and oral discomfort (odynophagia) exhibited by these patients responds well to phenobarbitone. There is no direct evidence linking phenobarbitone to saliva production but it does reduce small intestinal motility and could have local effects on the salivary glands (Plumb 1999; Vernau, Le Couteur & Maddison 2001). The effectiveness of the phenobarbitone may indicate that the primary cause of the condition is parasympathetic activation of salivary gland secretion. Three publications reported on surgical resection of the affected salivary glands, which failed to stop the hypersalivation and dysphagia until phenobarbitone was administered to the patients (Boydell *et al.* 2000a, 2000b; Kelly *et al.* 1979). This finding supports the theory that the sialorrhoea is part of a multifactorial parasympathetic response to an underlying stimulus or condition.

Steady state concentrations of phenobarbitone are only reached 18 days after the initiation of therapy (Vernau *et al.* 2001). Phenobarbitone, at the dosage levels and frequencies

used in the cases reported here and in the literature would thus not have reached steady therapeutic levels within the 2 days taken to see a clinical improvement. There is, as yet, no explanation for this phenomenon.

Patients with spirocercosis-induced dysphagia will, and do, show reduction of clinical signs with treatment of the underlying cause, but in some patients the degree of dysphagia precludes proper food intake and nutrition and the phenobarbitone therapy provides symptomatic relief whilst the nodule regresses. Unpublished data from the prospective trial show that the nodules will often reduce in size quite slowly. This finding is supported by a previous study in which it was reported that nodule regression in seven experimentally infected beagle dogs took between 35 and 544 days (Lavy *et al.* 2002).

Conclusion

Spirocercosis should be considered an important differential diagnosis for sialorrhoea in endemic areas. Our study showed that sialorrhoea occurs with an incidence of 11% in patients with spirocercosis in South Africa. Fox terrier and Jack Russell terrier breeds were predisposed to developing sialorrhoea concurrently with the *S. lupi*-induced oesophageal nodule, but the nodules in this breed were fewer and unlikely to be neoplastic at the time of diagnosis. Small-breed dogs were also predisposed to developing sialorrhoea concurrently with spirocercosis. Patients with sialorrhoea had statistically significantly fewer nodules although there was a large overlap between the two groups. There were no factors relating to the size, position, number and malignancy of the nodules that could be statistically correlated with the development of sialorrhoea. The histological evidence of hyperplasia, fibrosis and inflammation in the salivary glands was mild in most instances and these changes were also present in affected animals not displaying sialorrhoea. Treatment of dogs with spirocercosis showing severe sialorrhoea and odynophagia should include phenobarbitone to assist in the management of these patients.

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Competing interests

The authors declare that they have no financial or personal relationship(s) which may have inappropriately influenced them in writing this paper.

Authors' contributions

L.v.d.M. (University of Pretoria) was the project leader and was responsible for the project design, as a sub-section of a larger prospective patient study. Data were collected and collated by L.v.d.M. (University of Pretoria), E.D. (University of Pretoria) and J.C. (University of Pretoria). Preparation of the samples and analysis of histopathology was performed by S.J.C. (University of Pretoria). The data analysis was performed by L.v.d.M. (University of Pretoria) and E.D. (University of Pretoria). The article was written by L.v.d.M. (University of Pretoria) and J.C. (University of Pretoria) with E.D. (University of Pretoria) who performed the statistical reporting, and S.C. (University of Pretoria) the histopathological reporting.

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