PAPER

Pyrexia in juvenile dogs: a review of 140 referred cases

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OBJECTIVES: To describe the presentation, influence of previous treatment and diagnosis in juvenile dogs presenting with pyrexia to a UK referral centre.

MATERIALS AND METHODS: Clinical records of dogs aged 1 to 18 months presenting with a problem list including pyrexia (≥39·2°C) that was reproducible during referral hospitalisation were retrospectively reviewed. Signalment, history - including previous treatment, clinical examination findings and diagnosis were recorded. Diagnoses were categorised as non-infectious inflammatory, infectious, congenital, neoplastic and miscellaneous. The influence of previous treatment on the ability to reach a final diagnosis was analysed.

RESULTS: A total of 140 cases was identified. Diagnosis was reached in 115 cases. Non-infectious inflammatory disease was identified in 91 cases (79%), infectious disease in 19 cases (17%), a congenital disorder in four dogs (3%) and neoplasia in one dog (1%). Breeds most commonly identified were Border collies (17/140; 12%), beagles (16/140; 11%), Labrador retrievers (11/140; 8%), springer spaniels (9/140; 6%) and cocker spaniels (8/140; 6%). Before presentation, most dogs had received antibiotics (83/140; 59%), non-steroidal anti-inflammatory drugs (84/140; 60%) or steroids (9/140; 6%), either alone or in combination. Neither antibiotics nor non-steroidal anti-inflammatory drugs influenced the ability to reach a diagnosis. Steroid-responsive meningitis-arteritis comprised 55 of 91 (60%) individuals of the non-infectious inflammatory cohort. All four dogs diagnosed with congenital disorders were Border collies.

CLINICAL SIGNIFICANCE: Non-infectious inflammatory disease, particularly steroid-responsive meningitis-arteritis, immune-mediated polyarthritis and metaphyseal osteopathy, was commonly diagnosed in this population of pyrexic juvenile dogs.

INTRODUCTION

Pyrexia, or fever, in contrast to hyperthermia, is defined as an elevated body temperature that occurs due to alteration of the thermoregulatory set point in the anterior hypothalamus in response to endogenous or exogenous pyrogens (Doyle & Schortgen 2016). Pyrexia is a highly conserved physiological adaptive response that, in the short term, confers an evolutionary advantage, particularly when combating infectious disease (Kluger *et al*. 1996). The beneficial effects of pyrexia are well understood. In fact, use of antipyretics is controversial in critically ill people, in whom meta-analyses have demonstrated that, at best, their use may not influence outcome, and some studies have even identified increased morbidity and mortality in patients treated with antipyretic therapy (Kluger *et al*. 1996, Niven *et al*. 2013).

Pyrexia represents a challenge for the small animal practitioner, especially if signs are vague, suggesting numerous

differential diagnoses. Differential diagnoses can be categorised as infectious, non-infectious inflammatory (including immune-mediated), neoplastic and miscellaneous disorders. Studies have previously explored ultimate diagnoses in dogs and cats presenting with pyrexia, with the aim of guiding clinical suspicion and informing diagnostic test choices. Two previous studies have demonstrated that immune-mediated disorders were the most common cause of pyrexia, identified in 22% and 34·8% of dogs (Dunn & Dunn 1998, Battersby *et al*. 2006). A third study considered non-infectious inflammatory disease, including immune-mediated disease, as a single category; this was also the most common diagnostic category and was identified in 48% of dogs (Chervier *et al*. 2012). Interestingly, a recent study in cats found a high prevalence of infectious disease as a cause for pyrexia, which was identified in 38·7% of cases (Spencer *et al*. 2017).

In human medicine, diagnosis in children presenting with pyrexia of unknown origin (defined as unexplained pyrexia persisting for longer than 1 week) has been scrutinised separately from adults. Analysis has indicated the increased occurrence of infectious disease (51% compared with 35% adults) and decreased occurrence of neoplastic disease (6% compared with 11% in adults) and that children often reportedly improve despite no diagnosis or specific treatment (25% cases), with a presumed viral aetiology in these cases (Chow & Robinson 2011, Chusid 2017).

This study aimed to describe the characteristics of juvenile dogs (defined as those aged 1 to 18 months) presenting with pyrexia to a single referral hospital, particularly to explore age and breeds represented in this population, influence of previous treatment on the ability to achieve final diagnosis and final diagnosis. The intention was to help prioritise differential diagnoses and diagnostic tests when investigating and treating young dogs presenting with pyrexia.

MATERIALS AND METHODS

Case recruitment and data collection

The clinical database for dogs referred to the Small Animal Hospital between January 2009 and March 2018 was retrospectively searched to identify dogs aged 1 to 18 months presenting with pyrexia (≥39·2°C). To be included, pyrexia needed to have been identified at least once by the referring veterinarian and reproduced during hospitalisation in an attempt to exclude stress hyperthermia. Cases were excluded if records were incomplete.

Clinical records were examined, and details regarding signalment, history - including duration of signs before referral - and peak body temperature were recorded. Further diagnostic investigations, including imaging, cytology, histopathology and infectious disease screening (serology, culture and PCR), were performed at the attending clinician's discretion and recorded when undertaken. If a single dog presented on multiple occasions, the first presentation at which a diagnosis was recorded was captured, and additional presentations were excluded.

Classification of cases

After diagnostic investigations were completed, the dogs were retrospectively categorised to one of the following final diagnosis groups: non-infectious inflammatory disease including immune-mediated diseases; infectious disease; congenital disorders; neoplasia; miscellaneous disorders; and no diagnosis reached. If more than one disease process was diagnosed, the disease process attributed to be the cause of the pyrexia was classified. The exception to this was dogs diagnosed with a congenital disorder considered to predispose to an opportunistic infection, which was categorised as a congenital disorder as this was considered to be the underlying cause.

Influence of previous treatment

Treatment before referral was recorded. A large range of therapeutics was identified, and therefore, interventions were grouped as non-steroidal anti-inflammatory drug (NSAID) therapy, antimicrobials and corticosteroids. Therapy deemed "supportive" (opiate analgesia, gastrointestinal medications and intravenous fluid therapy) was not individually recorded for the purpose of analysis.

Outcome

Whether cases survived to discharge, were euthanased or died was noted. For cases that improved before a diagnosis was secured, time to temperature normalisation was also recorded.

Breed associations in non-infectious inflammatory conditions

Data from control dogs were collected to explore possible breed associations. This was performed for those with a diagnosis of non-infectious inflammatory disease due to small numbers in the remaining categories. Two controls were selected per study case. The database was searched for the date of presentation of each pyrexic dog, and the control dogs were selected as the previous and subsequent two juvenile dogs presenting for investigations of a disease process that was not associated with pyrexia.

Statistical analyses

Data were initially inputted into a spreadsheet (Microsoft Excel) and exported to a statistical package (IBM SPSS Statistics premium 24) for analysis. Data are presented descriptively. Continuous data were assessed for normality using the Kolmogorov–Smirnov test and presented with a mean±sd if normally distributed or median (range) if not. Following categorisation of diagnoses, the patient populations within these groups were compared for demographic differences using an independent t-test. The influence of previous therapy on whether a diagnosis was reached was explored using Fisher's exact test as appropriate. For all comparisons, P<0·05 was considered significant.

Breed associations were analysed for dogs with non-infectious inflammatory diseases if at least three individuals were included in this category. All other breeds were placed in an "other breed" category. Odds ratios were calculated using chi-squared analysis for the breed of interest *versus* all other breeds.

RESULTS

A total of 140 dogs were identified; no cases were excluded due to incomplete records (raw data available in Appendix S1, Supporting Information). Forty-five different breeds were represented (results shown in Table 1). Breeds with three or more individuals included beagle (n=19), Border collie (n=16), Labrador retriever (n=11), whippet (n=10), springer spaniel (n=9), cocker spaniel (n=8), lurcher (n=6), bulldog (n=5), Chihuahua (n=4), boxer (n=3), golden retriever (n=3) and shih-tzu (n=3). There were four cross-breed dogs. The mean age was 9·7±4·3 months. Most of the dogs were entire; 45 were female entire (32%), 26 were female neutered (19%), 48 were male entire (34%), and 21 were male neutered (15%). The duration of signs before referral was a median of 4 days (range 1 to 365 days). The peak temperature recorded was a mean of 40·2±0·6°C. The highest temperature recorded in any dog in this population was 41·8°C.

Classification of cases

A diagnosis was reached in 115 dogs. In the remaining 25 dogs, pyrexia resolved before investigations were completed in 24 dogs, and one dog was euthanased before a diagnosis was reached. In 21 of these 25 dogs, a provisional diagnosis of steroid-responsive meningitis arteritis (SRMA) was made based on clinical signs and signalment. Resolution was rapid in most dogs (occurred in 24 hours or less in 21 of 25 dogs).

Of the 115 dogs in which a diagnosis was made, 91 (79%) dogs had a non-infectious inflammatory condition. A large number of breeds were represented: those breeds with more than three individuals represented included beagle (n=14), Border collie (n=12), Labrador retriever (n=6), springer spaniel (n=6), whippet (n=6), cocker spaniel (n=5), lurcher (n=3), Chihuahua (n=3) and boxer (n=3). Fifty-five (60%) dogs with non-infectious inflammatory conditions, and 48% of dogs (in which a diagnosis was made) of these dogs were diagnosed with SRMA. Immune-mediated polyarthritis (IMPA) was identified in 15 dogs; four of these had concurrent dermatopathies (two juvenile cellulitis and two sterile neutrophilic dermatosis). Metaphyseal osteopathy (MO) was diagnosed in eight dogs, one of which had concurrent juvenile

cellulitis. Less common diagnoses included sterile pyogranulomatous lymphadenitis (n=4), immune-mediated neutropenia (n=2), meningoencephalitis (n=2), sterile neutrophilic dermatosis (n=4, two without concurrent non-infectious inflammatory disorder), juvenile cellulitis (n=4, one without concurrent non-infectious inflammatory disorder), meningomyelitis (n=1) and pancreatitis (n=1).

Nineteen dogs were diagnosed with an infectious disease. There was a large variety of breeds in this category. Diagnoses included abscess (n=5); pneumonia (n=4, three suspected secondary to aspiration and one bronchopneumonia); pyothorax (n=2); haemorrhagic gastroenteritis (n=2); and one each of canine respiratory coronavirus, leptospirosis, canine adenovirus, concurrent urinary tract infection and portosystemic shunt, septic peritonitis and septicaemia.

Four dogs were diagnosed with a congenital condition: trapped neutrophil syndrome with metaphyseal osteomyelitis (n=2) and congenital hypocobalaminaemia with opportunistic infection (n=2). All four dogs were Border collies. One bulldog was diagnosed with polyostotic lymphoma. Due to the low numbers of dogs with neoplastic and congenital conditions, comparisons were not performed with these groups.

Dogs with infectious diseases were significantly younger than dogs with non-infectious inflammatory disease (mean 7·2±3·8 months old compared with mean 10·0±4·5 months old, P=0·01), although there was considerable overlap of the age ranges in these groups (Fig. 1).

Influence of previous treatment

Eighty-four dogs (60%) received NSAIDs before referral for investigation, and 56 did not. There was no association between administration of NSAIDs before referral and ability to reach a definitive diagnosis (P=0·66). Nine dogs (6%) received corticosteroids before presentation. No further comparisons were performed with this group due to the infrequent administration of this therapy. Eighty-three (59%) dogs were treated with antibiotics before referral for investigation, and 57 were not. There was no association between the previous administration of antibiotics and the ability to reach a definitive diagnosis (P=0·12).

Table 1. Diagnosis in dogs, divided by breeds

Breed	Non-infectious inflammatory disease			Infectious	Congenital	Neoplasia	No diagnosis	Total
	SRMA	IMPA	Other					
Beagle	13	1	0	1	0	0	4	19
Border collie	5	4	3	0	4	0	0	16
Labrador Retriever	2	2	2	5	0	0	0	11
Whippet	4	1	1	0	0	0	4	10
Springer spaniel	6	0	0	2	0	0	1	9
Cocker spaniel	3	2	0	2	0	0	1	8
Lurcher	2	1	0	1	0	0	2	6
Bulldog	1	0	0	2	0	1	1	5
Chihuahua	3	0	1	0	0	0	0	4
Boxer	3	0	0	1	0	0	0	4
Golden Retriever	0	0	3	0	0	0	0	3
Shih-tzu	0	1	1	0	0	0	1	3
Other	13	3	10	5	0	0	11	42
Total	55	15	21	19	4	1	25	140

IMPA immune-mediated polyarthritis, SRMA steroid responsive meningitis-arteritis
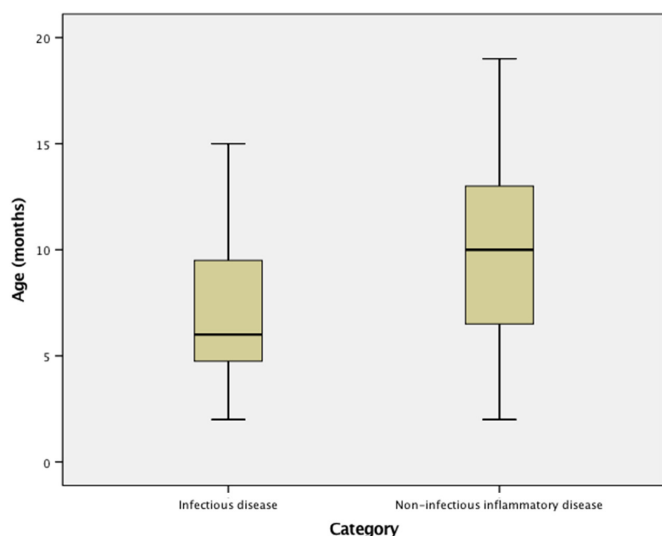
FIG 1. Age distribution of dogs with infectious and non-infectious inflammatory disease. The difference between the ages in these two groups was statistically significant, P=0·01

Outcome

Five dogs were euthanased: one dog before a diagnosis was reached, one with trapped neutrophil syndrome, one with polyostotic lymphoma, one with an abscess secondary to a migrating foreign body and one with immune-mediated neutropenia. Four dogs died, one with meningomyelitis, one with meningo-encephalitis, one with leptospirosis and myocarditis and one with bacterial pyothorax and pyopericardium secondary to migrating foreign bodies. The remainder (94%) survived to discharge.

Breed associations in non-infectious inflammatory conditions

Breed associations were examined in dogs presenting with non-infectious inflammatory conditions. Odds ratios were calculated for breeds for which more than three dogs were represented, using a control population of 280 dogs. Of these breeds, the beagle (OR 50·7 95% CI 6·6 to 391·9 P<0·001), Border collie (OR 2·7 95% CI 1·2 to 6·0 P=0·02), cocker spaniel (OR 4·6 95% CI 1·4 to 14·8 P=0·01) and whippet (OR 4·9 95% CI 1·3 to 17·7 P=0·02) were found to be over-represented.

DISCUSSION

Non-infectious inflammatory disease was over-represented in this referral population of pyrexic juvenile dogs and was identified in 79% of dogs in which a diagnosis was reached (65% of all cases). Previous studies examining dogs of all age groups (Dunn & Dunn 1998, Battersby *et al.* 2006, Chervier *et al.* 2012) have demonstrated the same bias towards non-infectious inflammatory conditions, particularly immune-mediated disorders (34·8%, 22% and 48% of dogs in each study, respectively), but this appears to be even stronger in this population of young dogs. An increased proportion of juvenile dogs diagnosed with non-infectious inflammatory disease relative to previous studies was commensurate with a decreased proportion of infectious (13·6% in this study compared with 25·8%, 16% and 18%) and, more intuitively, neoplastic diseases (one dog of 140 in this population compared with 7·6%, 9·5% and 6%). The proportion of dogs in which a diagnosis was not reached was comparable between our data and previous studies (17·8% compared with 22·7%, 19% and 28%). Interestingly, in all but one dog, the lack of a diagnosis in these 25 dogs was due to the resolution of clinical signs during hospitalisation, and SRMA was frequently recorded as the presumed diagnosis based on signalment and clinical investigation findings. This suspicion is supported by the well-established waxing and waning nature of immune-mediated disease, including SRMA (Tipold & Schatzberg 2010).

The most common disease diagnosed within the non-infectious inflammatory disease category was SRMA, representing almost half of all referred dogs in which a diagnosis was reached (55/115 dogs, 48%). This contrasts with reports by Battersby *et al.* (2006) and Dunn & Dunn (1998) in which seven of 66 dogs (11%) and no dogs of 101 dogs were diagnosed with SMRA, respectively. This preponderance of SRMA in juvenile dogs is not unexpected given that the typical age of onset is known to be less than 24 months (Scott-Moncrieff *et al.* 1992, Rose *et al.* 2014). Immune-mediated polyarthritis was identified in 15 dogs in this study (11%), with four having concurrent inflammatory dermatopathies, which is similar to the proportion of dogs presenting in all age groups (20 of 101 dogs, 20% in Dunn & Dunn 1998 and five of 66 dogs, 8% in Battersby *et al.* 2006) and is not unexpected given that IMPA is an immune-mediated disorder typically affecting young and middle-aged dogs (Clements *et al.* 2004, Rondeau *et al.* 2005).

Our results contrast with human medicine studies, in which children were identified to be more likely to suffer from infectious disease as a cause for pyrexia than adults. This difference may, in part, be explained by the low prevalence of endemic infectious diseases, reduced global movement of pet dogs and use of prophylactic vaccination in the UK dog population (Day *et al.* 2007) in comparison with studied child populations in which the infectious diseases most commonly reported were brucellosis, tuberculosis, typhoid fever, bartonellosis, leishmaniasis, urinary tract infection and osteomyelitis (Chusid 2017). Similar to our population of dogs suffering from infectious causes of pyrexia, pneumonia was an important cause and was identified in 23% of children with an infectious cause (Chow & Robinson 2011). In contrast to juvenile dogs, immune-mediated disorders represent a small proportion of children presenting with pyrexia, with 9% identified to be suffering from collagen vascular disorders (autoimmune disorders, including systemic lupus erythematosus, juvenile rheumatic arthritis and dermatomyositis) (Chusid 2017). This propensity to develop immune-mediated disease was not replicated in the recent study on cats (Spencer *et al.* 2017) and perhaps reflects immunological derangements unique to the developing dog that warrant further investigation. Similar to our study, a large proportion of children (23%) is reported to improve during the course of investigation of pyrexia (Chusid 2017).

Signalment and clinical investigation variables were compared between the different disease categories. This study identified dogs

presenting with infectious disease as being significantly younger (mean 7·2 months) than those with non-infectious inflammatory disease (mean 10·0 months), although the large overlap prevents this being clinically useful. Most dogs had a short duration of signs before referral (median 4 days), although unsurprisingly, those with congenital disease appeared to have a much longer, often lifelong, duration of signs. Survival rates were high in our whole study population, with 94% of dogs surviving to discharge.

Our study identified beagles, Border collies, cocker spaniels and whippets as over-represented in developing non-infectious inflammatory conditions. This corroborates the findings of Rose *et al.* (2014), in which beagles, Border collies, boxers, Jack Russell terriers, Weimeraners and whippets were over-represented in a cohort of dogs with SRMA and may be related to the high prevalence of SRMA diagnosis in this geographical location. Indeed, all the beagles in our study population were diagnosed with SRMA.

Treatment with NSAIDs and/or antimicrobials was common before referral: 80% of dogs had received either or both. In contrast to the report by Battersby and colleagues (2006), our study did not identify an influence of administration of NSAIDs or antimicrobial therapy on the likelihood of achieving a diagnosis. This difference may reflect the higher proportion of immune-mediated disease in our population, in which response to NSAIDs or antimicrobials would not be anticipated. Antipyretic therapy, including NSAIDs and acetominophen, is common in people with fever, particularly in children (Drwal-Klein & Phelps 1992). Large meta-analyses have failed to find evidence that treatment of the fever improves the course of illness and that, in critically ill patients, antipyretic therapy is controversial and sometimes contraindicated (Niven *et al.* 2013). This emphasises the important point that pyrexia is not the primary illness but a physiological mechanism that results from an inflammatory focus. Management should therefore be guided towards attempting to identify the source of pyrexia rather than providing symptomatic antipyretic therapy, especially as the latter appeared unlikely to be effective in this cohort of dogs.

This study has a number of limitations, particularly that the referral caseload may not reflect a representative population when extrapolated to the primary care caseload, and so, conclusions regarding this population must be interpreted with caution. In particular, referral in these juvenile dogs may have been driven by the refractory nature of their pyrexia, and perhaps NSAIDs and/or antimicrobials may prove more efficacious in a more heterogeneous population. In addition, therapy deemed supportive may in fact have influenced the ability to achieve a diagnosis; for example, opiate analgesia may have masked clinical signs such as neck pain in presenting dogs, with signs then resolving before investigation because of the waxing and waning nature of immune-mediated disease, including SRMA. In addition, referral may have been prompted by dogs with more vague signs rather than obvious infectious disease. A (well-founded) reluctance to perform CSF sampling in primary care practice may have biased our population towards SRMA. In dogs with resolving pyrexia, the diagnosis of "presumed SRMA" must be interpreted cautiously as this may have been subject to clinician bias rather than

an accurate diagnosis. Given that this study was single-centred and based in the United Kingdom, the preponderance of diagnosis of SRMA may be regional in nature. Rose *et al.* (2014) failed to identify a link between the geographical backgrounds of dogs with a diagnosis of SRMA, but the development of clinical signs and resulting referral may be a complex interplay between exposure to multifactorial environmental triggers in a patient with genetic predisposition and the circumstances of the primary care practitioner and owner.

In conclusion, clinicians should strongly consider non-infectious inflammatory disease, particularly SRMA, IMPA and metaphyseal osteopathy, in juvenile dogs with persistent pyrexia refractory to antimicrobial therapy and NSAIDs. In addition, in young, pyrexic Border collies with a lifelong history of clinical signs congenital disorders, including trapped neutrophil syndrome and congenital hypocobalaminaemia should be considered.

Conflict of interest

The authors have no conflicts of interest to disclose. The study obtained ethical approval (VIN/18/022).

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Supporting Information

The following supporting information is available for this article:

Appendix S1: Raw data.