**Description of neurological mimics presented to the neurology service of a referral small animal hospital.**

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Keywords: Incorrect referral, lameness, neurological examination.

Word count: 2825

Author contributions:

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P.W., contributed to the design of the study, collected and analysed data and co-wrote the paper. A.V., conceived and supervised the study and co-wrote the paper. P.F, provided access to the data and critical revision of the paper. S.M.M., G. H., contributed to the drafting of the paper. N.B., H.R., L.A., provided critical revision of the paper. P.W. and A.V. are responsible for the overall content as guarantors.

**ABSTRACT**

**Background:** Clinicians observe that cats and dogs referred to neurology services often do not have an underlying neurological disorder. There has been no analysis of the frequency or categorisation of these neurological mimics.

**Methods:** Retrospective study of 520 cases. Data on signalment, presenting clinical signs, neurological examination findings and final diagnosis was collected. Final diagnoses were classified as primary neurological, non-neurological in origin but with neurological clinical manifestation, completely non-neurological (neurological mimics) or undiagnosed. Presenting clinical signs and neurological examination results were compared between neurological mimics and primary neurological cases using Chi-square or Fischer exact test. Relative risk was calculated for significant associations.

**Results:** 74% were primary neurological conditions, 8% neurological mimics, 3% non-neurological with neurological manifestation and 15% undiagnosed. An animal referred for lameness was five approximately times more likely to be diagnosed as a neurological mimic than as a primary neurological disorder (Relative Risk, RR = 5.42, P < 0.001). Cases with a normal neurological examination were approximately 15 times more likely to be a neurological mimic (RR=14.97, P < 0.001).

**Conclusion:** Thorough examination with consideration of alternative diagnoses is important when a neurological condition is suspected in an animal that presents with lameness or normal neurological examination.

**INTRODUCTION**

In human medicine, the problem of incorrect hospital referral has been recognised; for instance, in one study 4% of patients had been referred by their general practitioner to an inappropriate hospital specialty [1]. Anecdotally, it has been observed within the neurology service at a veterinary referral teaching hospital that, relatively frequently, dogs and cats seen for initial consultations do not have a neurological condition, and then are transferred to another service. So incorrect referral also exists in veterinary medicine.

In both human and veterinary medicine, conditions mimicking specific neurological conditions have been studied [2-5]. Examples within veterinary medicine, including disorders mimicking intervertebral disc disease [6], epileptic seizures [7] and transient ischaemic attacks [8], have been investigated. However, information regarding conditions that can mimic neurological conditions in general is lacking. The authors believe it is important to study the incidence and characteristics of these neurological mimics as correct recognition and referral may speed up and target diagnostic tests and management, and might result in fewer costs for clients. This could improve the efficiency of the referral process and patient management.

The overall aim of this study was to investigate the frequency, aetiology and clinical characteristics of neurological mimics in small animal medicine. Specific aims were to quantify how often these presentations occur and to provide information on which particular cases are prone to be neurological mimics.

**METHODS**

**Data collection of cases**

The appointment list of all dogs and cats that presented to the Queen’s Veterinary School Hospital (QVSH), University of Cambridge, between 2017 and 2018 for a first referral to the neurology service was acquired from the hospital records. The medical records of these cases were then retrieved and the following data was recorded from the patient files: age, sex, breed, presenting clinical signs, neurological examination findings and final diagnosis. The presenting clinical signs were those defined by the referring veterinarian as the main complaints at the time of referral. The neurological examination result was recorded as ‘normal’ or ‘abnormal’ based on the QVSH neurologist’s assessment of all aspects of a regular neurological examination: the evaluation of the animal’s mentation, behaviour, posture, gait, postural reactions, spinal reflexes, cranial nerves as well as palpation. Each case was seen under the supervision of a board-certified neurologist.

**Classification of cases**

The final diagnosis stated in the report to the referring veterinary surgeon was used to classify conditions as (1) primary neurological, (2) non-neurological in origin but with neurological clinical manifestation, (3) non-neurological in origin or in clinical manifestation (neurological mimics) and (4) undiagnosed. The first category (primary neurological conditions), were defined as any disease originating from the nervous system itself, including both central and peripheral nervous systems. If multiple underlying problems occurred simultaneously, one of which was neurological in origin, the case was categorised as primary neurological, as it was considered referred to the correct department. The second category included cases that had a neurological clinical manifestation, but the origin of the disorder was not within the nervous system; for example, portosystemic shunt resulting in signs of hepatic encephalopathy. The third category did not involve the nervous system, with these referred to as neurological mimics: for example, when the final diagnosis was an orthopaedic disease. All neurological mimics were internally referred from neurology to another hospital service. Finally, if a definitive diagnosis was not reached, cases were categorised as ‘undiagnosed’. This consisted of cases for which no cause of clinical signs could be identified, as well as those with a suspected cause but no definitive diagnosis due to limited investigations or lack of follow-up data. By defining categories as such, and placing suspected diagnoses within the undiagnosed category, bias towards whether a condition was classed as neurological or non-neurological was avoided. The percentage of each category per total number of cases seen by the neurology department was calculated.

**Statistical analysis**

For statistical analysis, we compared primary neurological cases with neurological mimics, omitting non-neurological conditions with neurological clinical manifestation, with the aim to obtain a clear-cut distinction between true primary neurological cases and true non-neurological conditions, without the confusion of the overlap group. For categorical statistical comparisons, either the Chi-square test (for those with expected values of >5) or Fisher’s exact test (for those with values ≤ 5) [9] was used. P-values less than 0.05 were considered significant. When multiple factors were analysed, a Bonferoni’s correction to the P-value was applied [10]. Odd’s ratio and relative risk ratio, with confidence intervals, were calculated where significant associations were found. MATLAB ver. R2020a was used to create figures.

**RESULTS**

**Cases**

Data of 520 cases referred to the neurology service at the QVSH between 2017 and 2018 was available. Thirty-seven cats of 11 breeds (15 female and 22 male) and 483 dogs of 50 breeds (202 female and 281 male) between the ages of 12 weeks and 15 years old were seen, with a median age of eight years old for cats, and six years old for dogs.

**Case classification**

Primary neurological conditions accounted for 74% (n=386, 23 cats, 363 dogs) of cases, 3% (n=16, 4 cats, 12 dogs) of cases were non-neurological in origin but with neurological clinical manifestation, and 8% (n=42, 3 cats, 39 dogs) were considered neurological mimics. A final diagnosis was not reached in 15% (n=76, 7 cats, 69 dogs) of cases.

**Final diagnoses of non-neurological cases with neurological clinical manifestation**

The final diagnoses for cases categorised as non-neurological with neurological clinical manifestation consisted of otitis media/interna (31%, n=5, 1 cat, 4 dogs) presenting with vestibular signs, portosystemic shunt (19%, n=3, 3 dogs) presenting with signs of hepatic encephalopathy (such as epileptic seizures), insulinoma (13%, n=2, 1 cat, 1 dog), intoxication (13%, n=2, 2 dogs) and thiamine deficiency (6%, n=1, 1 cat) all presenting with an ‘abnormal behaviour’, hyperthyroidism suspected of predisposing to ischaemic myelopathy (6%, n=1, 1 cat) presenting with paresis, chronic kidney disease causing uraemia (6%, n=1, 1 dog) presenting with limb weakness and haemangiosarcoma of the mandible (6% n=1, 1 dog) presenting with Horner’s syndrome.

**Final diagnoses of neurological mimics**

The final diagnoses of neurological mimics were classified based on the department they were internally referred to. Sixty-seven percent (n=28, 1 cat, 27 dogs) were classified as orthopaedic, 26% (n=11, 2 cats, 9 dogs) as internal medicine and 7% (n=3 dogs) as ophthalmological conditions. The main orthopaedic diseases found included cruciate ligament disease (32%, n=9 dogs, three with secondary osteoarthritis), hip dysplasia (14%, n=4 dogs, three with secondary osteoarthritis) and immune-mediated polyarthritis (considered an orthopaedic disease rather than an internal medicine condition in this study) (14%, n=4 dogs), degenerative joint disease (14%, n=4) of the shoulder (n=1 dog), tarsus (n=1 cat), carpus (n=1 dog) and generalised (n=2 dogs). Others were a bone tumour (n=2 dogs), elbow dysplasia (n=1 dog), a non-vertebral fracture (n=1 dog, with secondary osteoarthritis), osteochondrosis dissecans (n=1 dog, with secondary osteoarthritis), and a tendinopathy (n=1 dog).

The main final diagnoses for the internal medicine cases included gastrointestinal diseases (36%, n=4: inflammatory bowel disease n=3 (1 cat, 2 dogs) and protein losing enteropathy n=1 dog), immune-mediated thrombocytopenia (18%, n=2 dogs) and hypoadrenocorticism (18%, n=2 dogs). Others were lymphoma (n=1 cat), a heart base mass (n=1 dog), hypothyroidism (n=1 dog) and paraphimosis (n=1 dog). The ophthalmological conditions diagnosed were sudden acquired retinal degeneration syndrome (67%, n=2 dogs) and progressive retinal atrophy (33%, n=1 dog). Some animals presented with more than one condition.

**Presenting clinical signs associated with neurological mimics**

Sixty-four percent (n=18 dogs) of neurological mimics classified as orthopaedic presented with lameness. Other presenting clinical signs of these cases included pain (14%, n=4 dogs), abnormal gait (11%, n=3 dogs), paraparesis (7%, n=2 dogs), abnormal posture, collapse, lethargy, muscle atrophy, stiffness and weakness (4% each, n=1 each dogs). Some animals presented with multiple clinical signs.

For each orthopaedic diagnosis with lameness, the number of cases with bilateral rather than unilateral lameness was recorded. Two cruciate ligament disease cases and two hip dysplasia cases were bilateral, no degenerative joint disease, elbow dysplasia, osteochondrosis dissecans, non-vertebral fracture or bone tumour cases were reported as bilateral; the tendinopathy case was unilateral. As cruciate ligament disease was the most common orthopaedic condition, further details of the cases were investigated in Supplementary Table 1.

Internal medicine conditions presented to the neurology department most commonly presented with pain (45%, n=5 dogs), weakness (27%, n=3 dogs), or weight loss (27%, n=3, 1 cat, 2 dogs). Other clinical signs for these cases included abnormal behaviour\*, abnormal gait\*, abnormal posture and involuntary movement (18% each, n=2, 2 dogs, \*1 cat), ataxia, exercise intolerance, lethargy, pyrexia and vomiting (9% each, n=1 dog). Ophthalmological conditions presented with blindness (67%, n=2 dogs) or abnormal behaviour (33%, n=1 dog). Some animals presented with multiple clinical signs.

To assess whether certain clinical signs were more commonly seen with neurological mimics than with primary neurological conditions, the main presenting clinical signs were compared between these two categories (Table 1). There was no significant statistical association between the presenting clinical sign and whether the final diagnosis was primary neurological or a neurological mimic, except for lameness (P <0.001). Lameness was determined to be 5.42 times more likely to be observed in neurological mimics than in primary neurological cases (Table 2).

 **Presence of neurological deficits in neurological mimics**

The neurological examination results for neurological mimics were compared to primary neurological cases to explore whether the absence of deficits would be associated with mimics. Most primary neurological cases (85%, n=316 (19 cats, 306 dogs) out of 374 (22 cats, 361 dogs)), had an abnormal neurological examination; not all cases had a neurological examination result recorded. Whereas most neurological mimics, 81% (n=34 dogs out of 42 (3 cats, 39 dogs)), had a normal neurological examination (P<0.001) (Supplementary Figure 1). Reasons for neurological mimics having an abnormal neurological exam are discussed later. Cases with a normal neurological examination were determined to be 14.97 times more likely to be a neurological mimic than primary neurological (Table 2).

However, primary neurological cases presenting with epileptic seizures often have a normal neurological examination within the inter-ictal period [11], and so an absence of neurological deficits is to be expected for these cases. Therefore, cases with a normal neurological examination, excluding those presenting with epileptic seizures, were determined to be 22.95 times more likely to be a neurological mimic than primary neurological.

Cases presenting with both the significant clinical sign of lameness and a normal neurological examination were determined to be 10.29 times more likely to be a neurological mimic (Table 2).

**Case signalment in neurological mimics**

Any trends in demographics that could help practitioners detect neurological mimics was investigated. No differences between categories in signalment (sex, age, breed or species) was visible (Supplementary Figures 2, 3, 4).

**DISCUSSION**

This is the first study that describes neurological mimics seen through a referral neurology service. While the majority of cases were correctly referred to the neurology service with a primary neurological diagnosis (74% of cases) or with neurological involvement (3%), 8% were considered non-neurological in origin (neurological mimics). An additional observation was that nearly 15% of all cases could not be given a final, definitive diagnosis.

Of the neurological mimics, most were classified as orthopaedic conditions. Unsurprisingly, orthopaedic cases often presented with lameness, which was the only clinical sign found to be significantly associated with neurological mimics compared to primary neurological cases. An animal referred for lameness was almost five times more likely to be later diagnosed as a neurological mimic, and therefore have an orthopaedic condition, rather than a primary neurological condition. Again, immune-mediated polyarthritis was considered an orthopaedic disease rather than an internal medicine condition in this study.

Cruciate ligament disease was the most common orthopaedic diagnosis. The authors expected the majority of animals diagnosed with orthopaedic conditions, especially cruciate ligament disease, to have bilateral disease and/or lameness contributing to the suspicion for a neurological rather than orthopaedic condition, however this was not the case. While 56% (n=5 out of 9) had bilateral disease (Supplementary Table 1), only 22% (n=2 out of 9) were determined to be bilaterally lame by the referring veterinary surgeon. Further information was obtained from the referral letters of cruciate ligament disease cases and some did mention a specific reason for referral to neurology: suspected lumbar spinal pain, suspected sacroiliac pain, suspected cervicothoracic disease, a previous neurological problem or no orthopaedic problem identified at the referring veterinary practice.

Consequently, careful orthopaedic examination should be performed in dogs presenting with lameness, including to try to determine true spinal pain and lateralisation of any lameness, before referral to a neurology service.

Internal medicine conditions often presented with vague clinical signs (such as apparent spinal pain, weakness, weight loss or abnormal behaviour) that can be associated with neurological conditions. It is postulated this could be why these cases were initially referred to the neurology service instead of internal medicine. Of the cases diagnosed with internal medicine conditions, the largest proportion were gastrointestinal diseases, including inflammatory bowel disease and protein losing enteropathy. The presentation of abdominal pain (such as kyphosis or apparent ‘spinal’ pain) was likely confused with a neurological condition, and may be why gastrointestinal disorders were referred to neurology. Ophthalmological conditions presented with blindness or abnormal behaviour due to developing blindness, this led to a reduced or absent menace response. There were too few cases to investigate how useful the pupillary light reflex could be in determining blindness to be peripheral rather than central.

As expected, most primary neurological cases had an abnormal neurological examination, whereas most neurological mimics had a normal neurological examination. Cases with a normal neurological examination were nearly 15 times more likely to be associated with neurological mimics, and nearly 23 times more likely if they did not present with epileptic seizures. In addition, cases with a normal neurological examination presenting with the significant clinical sign of lameness were approximately 10 times more likely to be a neurological mimic. Therefore, a thorough physical and neurological examination should be performed to help guide referral to the correct service.

The few neurological mimic cases that did have neurological deficits detected on neurological examination were investigated. These were found to be due to an incidental finding of proprioceptive deficits and a previously diagnosed neurological condition in two patients with internal medical conditions respectively, and absent menace response in those with an ophthalmological problem. Four patients with an orthopaedic diagnosis had mild proprioceptive deficits or decreased spinal reflexes due to previously diagnosed neurological conditions or incidental findings which the authors postulate may have been the reason for referral to the incorrect service for the new condition.

There are limitations to this study, which must be considered when interpreting the results. Only one referral hospital was used to source data, so variability in caseload between institutions is not considered. Data was collected over a two-year period, which limits the number and potentially variety of cases to only those that have presented in this timeframe. Data was not available for all cases over this time period, including some of the ‘undiagnosed’ cases, which could not be followed up to determine if further diagnostics did take place. Of these undiagnosed cases, there were more neurological mimics suspected, but could not be definitively diagnosed, and so the actual number of neurological mimics may be higher than we have recorded. In this study, we have not specifically looked at the implications of referral to the incorrect service, but we can only presume that referral to the incorrect department within a hospital might result in a delay of diagnosis and treatment. This has the potential to lead to less successful outcomes, extra stress for the patient and owners and additional consultation costs for the owners, possibly leading to more complaints.

Statistical analysis was done only between primary neurological conditions and neurological mimics to obtain the clearest results of differences in clinical characteristics between non-neurological conditions that mimic a neurological disease and true neurological conditions. But it has to be considered that there are overlap cases, such as non-neurological diseases with neurological presentation, where referral to the correct service might be more challenging and which might benefit from the input of multiple services.

This study is the first of its kind in veterinary medicine. Most likely, our results apply to more than one species. In this study, dogs and cats were simultaneously analysed, however, differences in presentation of neurological mimics between dogs and cats might have been missed, as only three cats were considered neurological mimics in this study. As different species have different diseases and thus might present differently, it would be interesting to further design studies that look into species-specific presentations of these neurological mimics.

This research supports the view that careful physical examination, including those of the musculoskeletal and nervous systems, with consideration of the differential diagnoses across disciplines is important to direct referrals to the correct department, especially when animals present with lameness, vague clinical signs, and/or no abnormalities on neurological examination. This study also highlights the benefits of a multi-disciplinary referral practice for optimising the management of patients.

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**TABLES**

Table 1: Presenting clinical signs for neurological mimics compared with primary neurological cases.

|  |  |  |  |
| --- | --- | --- | --- |
| **Clinical sign** | **Neurological mimic (n)** | **Primary neurological (n)** | **P-value** |
| Abnormal behaviour | 0 | 29 | 0.756 |
| Abnormal gait | 5 | 24 | 0.188 |
| Abnormal posture | 3 | 8 | 0.083 |
| Ataxia\* | 1 | 89 | 0.009 |
| Cranial nerve deficits | 0 | 8 | 1.000 |
| General signs | 9 | 36 | 0.029 |
| Incontinence | 0 | 6 | 1.000 |
| Involuntary movement | 2 | 12 | 0.650 |
| **Lameness** | **18** | **34** | **<0.001** |
| Miscellaneous | 0 | 8 | 1.000 |
| Muscle atrophy | 1 | 6 | 0.517 |
| Ophthalmological signs | 2 | 1 | 0.027 |
| Pain\* | 8 | 98 | 0.584 |
| Paresis\* | 2 | 79 | 0.038 |
| Plegia | 0 | 15 | 0.381 |
| Seizures\* | 0 | 60 | 0.014 |
| Stiffness | 1 | 5 | 0.464 |
| Vestibular signs | 0 | 30 | 0.059 |
| Weakness/exercise intolerance/collapse | 6 | 32 | 0.246 |

Chi-square test, or \*Fisher’s exact test. N = number of cases. ‘Abnormal gait’ was a change in gait that was not defined specifically as ataxia, paresis, weakness or lameness by the clinician. General signs include anorexia, inappetence, lymphadenomegaly, weight loss, lethargy, pyrexia and vomiting. Miscellaneous includes one or two cases each of coughing, difficulty opening the jaw, facial swelling, facial irritation, presence of a mass, panting and hypersalivation. ‘Incontinence’ includes both urinary and faecal. ‘Muscle atrophy’ localised to a limb or specific muscle group. ‘Ophthalmological signs’ includes blindness and enophthalmus. ‘Pain’ includes spinal and general pain. ‘Seizures’ = epileptic seizures. Significant findings (P ≤0.003) in bold.

Table 2: Odd’s Ratio and Relative Risk for different variables associated with neurological mimics rather than primary neurological conditions.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable associated with neurological mimics rather than primary neurological conditions** | **P-value** | **OR** | **OR 95% CI** | **RR** | **RR 95% CI** |
| Lameness | **<0.001** | 7.76 | 3.84 - 15.71 | 5.42 | 3.17 - 9.29 |
| Normal neurological examination | **<0.001** | 23.16 | 10.20 – 52.54 | 14.97 | 7.18 – 31.20 |
| Normal neurological examination not presenting with seizures | **<0.001** | 51.65 | 21.69 – 123.02 | 22.95  | 11.18 – 47.11 |
| Normal neurological examination presenting with lameness | **<0.001** | 80.0  | 12.07 - 530.3 | 10.29  | 3.44 - 30.80 |

OR = Odd’s Ratio, RR = Relative Risk, CI = Confidence Intervals. Significant P-values in bold, P<0.05.

**FIGURE LEGENDS**

Figure 1: The total number of clinical signs observed over all cases divided into categories based on their final diagnosis. ‘Pain’ includes spinal and general pain. ‘Seizures’ = epileptic seizures. General signs include anorexia, inappetence, lymphadenomegaly, weight loss, lethargy, pyrexia and vomiting. Miscellaneous includes cough, difficulty opening the jaw, facial swelling, presence of a mass, panting, facial irritation and hypersalivation. ‘Ex intol’ = exercise intolerance. ‘Abnormal gait’ was a change in gait that was not defined specifically as ataxia, paresis, weakness or lameness by the clinician. ‘Muscle atrophy’ localised to a limb or specific muscle group. ‘Incontinence’ includes both urinary and faecal. ‘Ophthalmological signs’ includes blindness and enophthalmus. Lameness is over-represented in neurological mimics, highlighted by the arrow and circled.

Supplementary Table 1: Details of orthopaedic cases diagnosed with cruciate ligament disease. HL = hindlimb.

Supplementary Figure 1: Neurological examination result of neurological mimics and primary neurological conditions.

Supplementary Figure 2: The sex and neuter status of animals with a primary neurological or neurological mimic diagnosis.

Supplementary Figure 3: The age of animals (in years) with a primary neurological or neurological mimic diagnosis. ‘X’ year old includes all animals aged from ‘X’ year 0 months to ‘X’ year 11 months old.

Supplementary Figure 4: Classification of neurological mimics into cats and breed of dog, compared to the number of these cases with a primary neurological diagnosis. WHWT = West Highland White Terrier, SBT = Staffordshire Bull Terrier, GSD = German Shepherd Dog. From left to right dog breeds are ordered roughly by increasing weight, followed by crossbreeds and cats. Due to the smaller number of cats, their breeds were not analysed separately in the figure. Primary neurological cases consisted of Domestic Shorthair (n=13), British Shorthair, Domestic Longhair and Maine Coon (n=2 each), Ragdoll and Scottish Fold (n=1 each). Neurological mimics were Domestic Shorthair (n=2) and Ragdoll (n=1).