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Title:
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Date:
2018-11-01

Citation:
Martinez-Anton, L., Marenda, M. S., Firestone, S. M., Bushell, R. N., Child, G., Hamilton, A. I., Long, S. N. & le Chevoir, M. A. R. (2018). Response from Dr. Martinez-Anton, et al. to Dr. Foster letter to editor regarding Investigation of the role of Campylobacter infection in suspected acute polyradiculoneuritis (APN) in dogs. Journal of Veterinary Internal Medicine, 32 (6), pp.1843-1845. https://doi.org/10.1111/jvim.15328.

Persistent Link:
https://hdl.handle.net/11343/271352

Received: 23 August 2018 | Accepted: 23 August 2018

DOI: 10.1111/jvim.15328

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

LETTER TO THE EDITOR

Response from Dr. Martinez-Anton, et al. to Dr. Foster letter to editor regarding Investigation of the role of *Campylobacter* infection in suspected acute polyradiculoneuritis (APN) in dogs

Dear Editor,

Thank you for the opportunity to respond to the letter from Dr. Foster regarding our recent publication "Investigation of the role of Campylobacter infection in suspected acute polyradiculoneuritis (APN) in dogs."

Dr Foster's main concern about the paper was the inclusion criteria. Our inclusion criteria were similar to previously published papers about acute polyradiculoneuritis (APN) in dogs.[1–3] There is no definitive diagnostic test available for dogs with APN. It is a diagnosis made on the basis of clinical signs and clinical course. Further testing such as electrodiagnostic investigation and cerebrospinal fluid (CSF) analysis provides further supporting evidence but these tests do not provide a definitive diagnosis; and negative or positive results are not diagnostic. This is the reason why we have used the term "suspected APN" in this investigation. Other diagnostic tests such as biochemistry and serology are performed to rule out other diseases; however, considering the main differential diagnoses in acute LMN diseases, we do not believe these tests are mandatory for the inclusion criteria. The main differential diagnoses for acute onset of LMN disease in dogs are myasthenia gravis, botulism, tick paralysis (in some Australian states and North America), and death from adder envenomation (in Australia). All were considered very unlikely in our cases considering their history, clinical course, and neurological examination, including the lack of autonomic signs and mild cranial nerves involvement.[4] Moreover, as explained in the paper, a thorough tick search was performed and found to be negative in all the APN dogs. In Australia, this is routine in dogs presenting with acute onset of LMN signs. Based on these, we respectfully disagree with the statement that our inclusion criteria were insufficient for a diagnosis of APN or the suggestion of tick search being required as part of the inclusion criteria.

Regarding Dr Foster's comment about the inclusion criteria of "ascending LMN": *four cases had descending tetraparesis and four cases had all limbs affected. Thus, 30% of the APN cases in this study did not appear to meet the inclusion criteria of the study*, we agree that using the term "ascending" may cause confusion as with APN, all forms should be considered; ascending, descending, and all limbs at the same time. Therefore, it would be more appropriate to use "rapid development of LMN" to avoid confusion.

Dr Foster cited that *snake envenomation is another common cause for lower motor neuron signs in Australian dogs.* We agree that paralysis and weakness have been reported in snake envenomation in Australia; however, the clinical presentation tends to be very different from dogs with APN. Ataxia is more common than progressive LMN tetraparesis, and these dogs are usually systemically affected including mydriasis, acute collapse, vomiting, ptyalism, dyspnea, reduced gag reflex, and pigmenturia.[5] The most common snake species in the geographic area described are eastern brown snakes, mainland tiger snakes, Red bellied black snakes, and death adders. Brown snake envenomation is associated with a very rapid onset of neurologic signs and coagulopathy not evident in any cases included. Black snake and tiger snake envenomation causes significant rhabdomyolysis and pigmenturia also not evident in any of the cases. Death adder envenomation is very rare in urban areas and is characterized by rapid onset of LMN signs, which is rapid involvement of the cranial nerves and often respiratory failure. This was not observed in any of our cases.

Dr Foster cited that *with each case of APN enrolled, the study design was such that two case controls were to be recruited from staff and client dogs yet only 47 control dogs were included not 54 as there should have been for 27 APN cases; that is there were 13% fewer controls than specified in the study design. There was no mention of why this deviation from the study design occurred.* We would like to clarify this from the statistical point of view. A priori sample size calculations were undertaken based on best available evidence. As the study progressed, it became clear that a very strong magnitude association was present and many fewer dogs than the prior estimates would be required. Post hoc sample size re-estimation suggests that the power to detect the reported odds ratio of 9.4 may be achieved with only 14 cases and 28 controls. Given the extreme magnitude of the detected association, the minor discrepancy focused on by Dr Foster between what was intended and what was undertaken is completely irrelevant.

Dr Foster also presented a few concerns that we would like to address individually as follows:

1. *there was no information on the clinics, number of clinicians involved or their levels of expertise (a relevant issue when the inclusion criteria is based on clinical assessment)*

The clinics involved were the University of Melbourne Veterinary Teaching Hospital and the Small Animal Specialist Hospital in Sydney. Each of the 27 dogs with suspected APN were examined at some stage by boarded neurologists: GC (DipACVIM-Neurology), SL (DipECVN), or MLC (DipECVN). We would argue that specialist neurologists would be best placed to be able to distinguish between different neuromuscular syndromes when making a diagnosis based on clinical signs.

2. *there was no information on how many cases were from NSW and how many from Victoria (potentially different incidence of tick paralysis and snake species)*

   Two cases were from NSW. As explained previously, tick paralysis and snake envenomation are significantly different clinical syndromes when compared to acute polyradiculoneuritis (see final paragraph for further discussion).

3. *three dogs with APN (11%) did not have a questionnaire available for analysis*

   For these 3 cases, only the information available from the dog's clinical record was used. So, questions from the questionnaire remained unanswered despite these records but as stated in the paper, *based on their history in the clinical database, details relative to the diet were available for all APN cases.*

4. *there was no record of how many staff dogs were used as controls relative to client dogs and this could be a significant source of bias given that staff of veterinary clinics that have a strong belief that raw chicken causes APN could potentially be less likely to feed raw chicken*

   There were 16 staff dogs and 31 client-owned dogs. Before the analysis of data, no staff were made aware of the hypothesis associating a diet containing raw chicken with the development of APN.

5. *Question 4 of the survey asked whether the dog was indoors, outdoors or both with clarification of whether dogs were primarily outside, primarily inside or a mixture. That information was not recorded in the results. Table 1 however indicates that a high number of dogs in both groups had no outdoor access. It seems implausible that 16/24 APN dogs and 20/47 control dogs had no outdoor access. This would imply that the majority of dogs in this study were not taken outside to defaecate, urinate or eat their raw bones*

   When we asked owners whether dogs were primarily outdoor, indoor, or both, we recorded this information and summarized it in a binary yes or no question for statistical analysis. We would like to clarify that those dogs recorded as *no outdoor access* were those living indoors, which allowed for those taken outside for supervised walks.

6. *Question 8 of the survey questionnaire requested details of raw meat but no details were provided in results (Table 1) as to the sources so it is not known whether raw chicken was the only source of raw meat?*

   This is recorded in Table 1, 26/27 APN cases had raw chicken. None of these dogs had access to any other type of raw meat.

7. *it is not possible from the paper to assess how many of the control dogs positive for Campylobacter spp received raw chicken and this is particularly relevant given the study aims.*

   Among the 11 controls that tested Campylobacter positive, 4 reportedly consumed raw chicken. In comparison, all 13 of the case dogs that were positive for Campylobacter had consumed raw chicken. As presented in Supporting Information Table S5, there is a strong association between campylobacteriosis and raw chicken consumption in the study population. It is not possible to stratify these results by *Campylobacter* species, which could be very meaningful in a larger study, because campylobacteriosis from raw chicken consumption would be expected to be more strongly associated with *Campylobacter jejuni* than *Campylobacter upsaliensis.*

8. *sequencing for species determination in this prospective study was performed in 77% (10/13) of Campylobacter positive APN samples but only 45% (5/11) of Campylobacter positive control samples*

   Sequencing was performed to add more information about the Campylobacter species involved in our positive cases. However, this was not a requirement in our investigation and it was only recorded when available. In some cases, there was not enough sample or the sequencing did not work.

9. *C. upsaliensis was predominantly identified in this study. The authors state that C. upsaliensis has only ever been reported in three cases of human Guillain Barré syndrome (GBS). Given that there was incomplete sequencing information and no difference in prevalence of C jejuni (a known cause of human GBS, the model for this hypothesis) between the groups, any association between Campylobacter and APN in dogs seems tenuous.*

   The authors are unclear as to what Dr Foster is suggesting here. Initially, she suggests that *C. upsaliensis* has only been rarely implicated in GBS (and therefore by association would appear to be an unlikely cause in dogs) but then suggests that overall there is a tenuous link between the presence of any campylobacter and APN in dogs. The authors would most strongly disagree with this second point—we believe the epidemiological evidence for an association between the identification of campylobacter and the development of APN is compelling based on the odds ratios presented. It remains unclear whether the particular species that we identified most commonly (*C. upsaliensis*) is a sufficient cause on its own for APN. For some cases, short-lived episodes of *C. jejuni* infection may have occurred and because of sampling delays only *C. upsaliensis* was detected. Nonetheless, the evidence of the study accords well with published reports that *C. upsaliensis* has been reported to be associated with GBS in people, making it a plausible candidate in dogs.

10. *there was an unsubstantiated comment that small breed dogs are more likely to eat raw chicken (necks and wings), thus the association between small breeds and APN. It is important to alert readers that it is also very common practice in Australia to feed whole raw chicken frames to large breed dogs with most supermarkets, in WA at least, selling chicken frames for this purpose in the chilled meat section*

    We can only comment based on our clinical experience, and we have not seen large breed dogs being fed whole raw chicken frames as a common practice in this geographic area. We have seen small breed dogs being fed small bones more often than large breed dogs. This hypothesis is merely stated as a one potential, albeit we consider highly likely explanation for this

finding. A potential alternative explanation would be an unknown genetic factor.

11. *limitations of the study were not acknowledged and there were no alternative explanations proposed for any of the associations:*

- *for example, it may be that animals eating raw chicken were more likely to be fed other raw meat and that those other meats could be the cause of Campylobacter positivity or neurological signs*

We believe that in our study this is unlikely, considering that all the APN cases that fed raw meat were fed only with raw chicken, not other type of meat (please see answer to comment 6 above).

- *for example, it may be that dogs (especially small breed dogs) eating raw chicken are eating outside and acquire a novel mosquito-borne disease, experience snake or spider envenomation (flaccid paralysis in cats in Sydney, NSW has anecdotally been attributed to spider envenomation) or develop tick paralysis. The latter is particularly relevant given that Ixodes holocyclus could be a potential explanation for the increased incidence of APN in NSW and Vic compared to the rest of the world and other states in Australia, such as WA, where Ixodes holocyclus is not found.*

There is no published data to support spider envenomation or mosquito vector borne viral disease as a cause of acute polyneuropathy in dogs in Australia. To the best of our knowledge, the only published data about the effect of Sydney-funnel web spider in dogs and cats[6] reported that the effects were confined to the cardiovascular system including transient moderate hypertension, tachycardia, and atrial fibrillation.

It would be expected, however, that if other causes associated with being outside were responsible for the development of APN, these factors would be common to both groups. Because a diet containing raw chicken was the only single significant risk factor identified associated with APN, these alternative hypotheses seem implausible.

Our questionnaires did not include questions regarding these hypothetic trigger agents. Moreover, it appears to us that it would be very difficult for dog owners to comment on the probability of such events (mosquito or spider bites). Tick paralysis is extremely rare in Victoria. U-Vet hospital is one of the few places that hold tick antivenom around Melbourne and as a result has a much higher caseload than the rest of the state. Nine confirmed cases of tick envenomation and subsequent tick paralysis syndromes were recorded in our hospital over the time our study was conducted. Seven of these had recently traveled in New South Wales and had returned from an area where *Ixodes holocyclus* is endemic. Except for the 2 cases from NSW, none of our APN cases had evidence of a travel history that involved being in an *Ixodes*-endemic area. All the tick paralysis cases had a positive tick search that helped to locate at least one tick and often several. As previously stated, all our APN cases had a thorough tick search conducted that was negative. Finally, all tick paralysis cases had moderately to severely increased respiratory effort. In comparison, none of our APN cases had respiratory compromise.

We would like to state that these are some of the aspects that clinically distinguish tick paralysis from APN and the same applies to botulism and snake envenomation. All the above-cited conditions have been described in association with some degree of ascending LMN paresis/paralysis, however the patients' history and clinical assessment are diverge enough from those expected with these diseases that our inclusion criteria were considered to have ruled out these other conditions.

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