


## Standard Article

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Investigation of the Role of *Campylobacter* Infection in Suspected Acute Polyradiculoneuritis in DogsL. Martinez-Anton , M. Marena, S.M. Firestone, R.N. Bushell, G. Child, A.I. Hamilton, S.N. Long, and M.A.R. Le Chevoir

**Background:** Acute polyradiculoneuritis (APN) is an immune-mediated peripheral nerve disorder in dogs that shares many similarities with Guillain-Barré syndrome (GBS) in humans, in which the bacterial pathogen *Campylobacter* spp. now is considered to be a major triggering agent. Little information is available concerning the relationship between APN and *Campylobacter* spp. in dogs.

**Hypothesis/Objectives:** To estimate the association between *Campylobacter* spp. infection and APN. Associations with additional potential risk factors also were investigated, particularly consumption of raw chicken.

**Animals:** Twenty-seven client-owned dogs suffering from suspected APN and 47 healthy dogs, client-owned or owned by staff members.

**Methods:** Case-control study with incidence density-based sampling. Fecal samples were collected from each enrolled animal to perform direct culture, DNA extraction, and polymerase chain reaction (PCR) for detection of *Campylobacter* spp. In some cases, species identification was performed by sequence analysis of the amplicon. Data were obtained from the medical records and owner questionnaires in both groups.

**Results:** In cases in which the fecal sample was collected within 7 days from onset of clinical signs, APN cases were 9.4 times more likely to be positive for *Campylobacter* spp. compared to control dogs ( $P < 0.001$ ). In addition, a significant association was detected between dogs affected by APN and the consumption of raw chicken (96% of APN cases; 26% of control dogs). The most common *Campylobacter* spp. identified was *Campylobacter upsaliensis*.

**Conclusions and Clinical Importance:** Raw chicken consumption is a risk factor in dogs for the development of APN, which potentially is mediated by infection with *Campylobacter* spp.

**Key words:** Acute polyradiculoneuritis; *Campylobacter*; Dogs; Raw chicken.

Acute or idiopathic polyradiculoneuritis (APN) is the most frequently identified acute generalized peripheral neuropathy in dogs worldwide and is characterized by acute onset of lower motor neuron (LMN) signs.<sup>1</sup> The initial clinical signs typically develop in the pelvic limbs with a rapid ascending progression to involve the thoracic limbs, causing a flaccid LMN tetraparesis or tetraplegia. It is an immune-mediated disorder affecting the ventral spinal nerve roots more

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## Abbreviations:

Abs	antibodies
APN	acute polyradiculoneuritis
CadF	<i>Campylobacter</i> adhesion to fibronectin
CSF	cerebrospinal fluid
CK	creatine kinase
CSM	charcoal-based selective medium
GBS	Guillain-Barré syndrome
IFAT	indirect fluorescent antibody test
LMN	lower motor neuron
SBA	sheep blood agar
T4	thyroxine

severely, with minimal dorsal nerve root involvement.<sup>1–6</sup> Cranial nerve involvement occurs in 80% of affected patients. The most commonly affected cranial nerve is the vagal nerve, causing dysphonia.<sup>7</sup>

Acute polyradiculoneuritis in dogs has been proposed as a canine model of Guillain-Barré syndrome (GBS) in humans.<sup>1–7</sup> This consideration initially was based on clinical, electrophysiological, and pathological similarities. The histopathological changes described in dogs with APN are similar to those of patients suffering from the demyelinating form of GBS (acute inflammatory demyelinating polyradiculoneuropathy or AIDP). Recently, the presence of anti-GM2 ganglioside antibodies (Abs) in dogs affected by APN has been demonstrated, reinforcing the hypothesis that APN is the canine counterpart of GBS.<sup>7</sup>

Acute polyradiculoneuritis was first described in North America in dogs used to hunt raccoons and may have occurred as a result of contact with racoon saliva, hence

the original term “coonhound paralysis”.<sup>8</sup> Since then, this disease has been identified in many other countries with no natural racoon population.<sup>3</sup> Other suspected risk factors include recent vaccination and upper respiratory and gastrointestinal infections.<sup>1–4</sup> In GBS, infection by the bacterial pathogen *Campylobacter* now is considered a major triggering agent, with up to 40% of GBS patients reported as having *Campylobacter jejuni* infection 1–2 weeks before the onset of GBS.<sup>9,10</sup> Other infectious agents have been found to be associated with GBS including *Haemophilus influenzae*,<sup>11</sup> *Mycoplasma pneumoniae*,<sup>12</sup> cytomegalovirus,<sup>13,14</sup> Epstein-Barr virus,<sup>14</sup> *Borrelia burgdorferi*,<sup>15</sup> and, most recently, Zika virus.<sup>16</sup> Cases of GBS after rabies and swine influenza vaccines also have been reported.<sup>17–19</sup> To our knowledge, no dog in Australia has been reported to be infected by any of these agents.

Most *Campylobacter* cases in humans are considered to be associated with consumption of raw or undercooked poultry. Consumption of contaminated water and unpasteurized milk also play important roles. Chickens are a natural reservoir of *Campylobacter*, where the bacteria colonize the mucosal layer of the gastrointestinal tract and can be transferred between chickens by the fecal-oral route.<sup>10,20</sup> We have observed that it is common practice for Australian dog owners to feed their dogs raw chicken as part of their daily diet or simply as a treat. Thus, we are under the impression that the prevalence of raw chicken consumption is very high in the population of APN dogs that they have diagnosed or treated and that the incidence of APN is possibly higher in Australia than in other countries.

We undertook a case-control study primarily to investigate the association between *Campylobacter* infection in dogs and APN to determine whether *Campylobacter* could be a trigger for APN. Another aim of our study was to identify potential risk factors associated with APN, including consumption of raw chicken meat and recent *Campylobacter* infection.

## Materials and Methods

### Animals and Data Collection

This case-control study was conducted at the University of Melbourne Veterinary Teaching Hospital (U-Vet hospital) between March 2015 and February 2017. Cases originated from 2 contiguous Australian states (Victoria and New South Wales). Data on potential explanatory variables and clinical specimens were collected from dogs affected by APN (cases) and were compared to a group of healthy dogs (controls). Dogs from both groups were recruited over the duration of the study period in an incidence density-based sampling strategy (ie, as each case was recruited, 2 controls were recruited) with very coarse frequency matching by dog size (so that this variable could still later be analyzed for associations with case-control status). Considering that the prevalence of *C. jejuni* in clinically normal dogs appears to be higher in dogs <6 months of age, we included only dogs >1 year of age in both groups.<sup>20,21</sup>

Acute polyradiculoneuritis is diagnosed based on characteristic clinical signs and clinical course, supportive diagnostic tests, and by exclusion of other causes of generalized weakness. Inclusion criteria for the APN group were acute onset of ascending LMN signs ≤3 weeks before presentation and no evidence of possible exposure

to botulism neurotoxin. In addition, hematology and biochemistry (including creatine kinase [CK] activity and serum potassium concentration, n = 23), cerebrospinal fluid (CSF) analysis (n = 7), indirect fluorescent antibody tests (IFAT) for *Toxoplasma gondii* (n = 4) and *Neospora caninum* (n = 8), serum total thyroxine (T4) concentration (n = 11), acetylcholine receptor antibodies (n = 12), and electrodiagnostic examination (n = 9) also were considered and performed when available. However, these tests were not a requirement to be included in the disease group.

The control group included dogs defined as healthy based on history and physical examination. The animals were either client-owned or pets owned by staff members. Dogs were excluded from the study if they were receiving any medication at the time of enrollment or up to 1 month before the study, with the exception of vaccinations and prophylactic antiparasitic therapy. Informed consent was obtained from all owners before study enrollment, and the project was approved by the Animal Ethics Committee of the University of Melbourne, Australia (AEC number 1513717).

Demographic, environmental and dog lifestyle factors were investigated as potential risk factors. Data were obtained from the medical records, and owner questionnaires were undertaken in both groups. These questionnaires were available in every case to collect data relative to the dog's environment and way of living for epidemiological analysis. A section in the questionnaire to collect details regarding the natural course of the disease also was available for the APN group (Data S1 and S2).

### Sample Collection and Laboratory Methods

Paired fecal samples, swabs, or both were collected from each enrolled animal to perform initial direct culture within 24 hours. All cultures were performed under microaerophilic conditions using the CampyGen 3.5 system.<sup>a</sup> One fecal sample or swab was plated directly on a selective medium, *Campylobacter* charcoal-cased selective (CSM) agar. The additional fecal sample or swab was inoculated into Bolton broth for selective enrichment and incubated at 37°C for 24 hours. A second CSM agar plate then was inoculated with a loopful of the Bolton broth. The CSM plates were incubated at 37°C and were examined for growth after 24 and 48 hours. Suspect colonies were purified on sheep blood agar (SBA), and subcultures were identified at the genus level by growth characteristics and microscopy. The remainder of the Bolton broth and fecal samples were stored at –20°C. Genomic DNA extraction was performed directly from the fecal sample or swab, from Bolton broth enrichment cultures, and from purified bacterial isolates using a silica-based column method.<sup>22</sup> Purified genomic DNA preparations were stored at –20°C. *Campylobacter* identification was performed using molecular identification methods. All suspect *Campylobacter* bacterial isolates, Bolton broth, and fecal DNA extracts were screened for the presence of *Campylobacter* spp, 16S DNA by polymerase chain reaction (PCR) which was performed on approximately 100 ng of genomic DNA as previously described.<sup>23</sup> We considered *Campylobacter*-positive samples to be those positive on culture, PCR, or both. The *cadF* gene also was detected by PCR as described previously.<sup>24</sup> *Campylobacter* that were *cadF* positive were differentiated as *C. jejuni* or *Campylobacter coli*. However those isolates, together with all of the other *Campylobacter* isolates, also were identified by 16S ribosomal DNA sequencing. The 16S rDNA was amplified by PCR using Bioline MyTaq mix<sup>b</sup> and 20 μM of each of the primers 27F (AGAGTTTGATCMTGGCTCAG) and 1492R (TACGGYTACCTTGTTACGACTT)<sup>25</sup> and approximately 50 ng of genomic DNA. The reaction was subjected to 35 cycles of 95°C for 30 seconds, 55°C for 30 seconds, and 72°C for 90 seconds with a final extension of 5 minutes at 72°C. Sanger sequencing of the gene was performed by the Australian Genome Research Facility on a purified PCR product capturing approximately 1,100 bp including the

hypervariable V3 region using primers 341F (CCTACGGG AGGCAGCAG) and 907F (AAACTCAAAGGAATTGA CGG).<sup>25,26</sup> A contig of the overlapped sequences was compared with the curated databases of EzBioCloud<sup>27</sup> and the Ribosomal Database Project,<sup>28</sup> and sequence-based identification was confirmed with sequence similarity cutoff values set at 97 and 99% for genus and species level, respectively.

### Statistical Analysis

Frequency cross-tabulations were prepared of APN cases and controls by each of the putative risk factors. Odds ratios (OR), 95% confidence intervals (CI), and *P*-values were first estimated using univariable exact logistic regression. This approach is well suited to modeling binary outcome variables for small sample size datasets, when some of the cells formed by the outcome and categorical predictor variable(s) have no observations or both situations.<sup>29</sup> Exact logistic regression provides ORs, the desired measure of association for a case-control study. To further investigate the effect of sampling delays, the association between *Campylobacter* spp. positivity, and APN status, the case definition was restricted to include only cases for which sampling occurred within 10, 7, and 4 days, respectively, of clinical onset of APN (represented by the variables, *Campylobacter* spp. positive <10, <7, and <4 days, respectively). Variables with <10% missing data and associated with the outcome in univariable analysis at *P* < 0.25 were considered for multivariable analyses. A putative causal diagram was developed a priori in Dagitty<sup>30</sup> to guide multivariable analysis, considering that several of the exposure variables, if causal, could be acting through the same pathway (such as raw meat consumption, raw chicken consumption, and *Campylobacter* spp. positivity). Modeling proceeded using a manual backward stepwise approach, considering the minimum adjustment set for the stated hypothesis of most interest (testing the association between positivity to *Campylobacter* spp. and APN case status), and continued until only variables statistically significant at *P* < 0.05 were retained in the final model. Given the small sample size, no interaction terms were tested.

### Results

The APN group included 27 dogs, with 19 females (15/19 neutered) and 8 males (5/8 neutered). Mean age at the time of study enrollment was 7.4 years (standard deviation [SD], 3.6), and median weight was 8.5 kg (range, 3.8–25 kg). Cases occurred evenly throughout the year, and breed distribution was as follows: Maltese (7), Poodle (6), Jack Russell Terrier, and Griffon Bruxellois (2 each) and Fox Terrier, Silky Terrier, Labrador Retriever, Cocker Spaniel, Golden Retriever, Border Collie, Beagle, Pomeranian, German Shepherd, and Miniature Schnauzer (1 each). The control group included 47 healthy dogs, with 31 females (28/31 neutered) and 16 males (12/16 neutered). Mean age was 6.7 years (SD, 3.2) and median weight was 14 kg (range, 3.0–46 kg). The breed distribution was as follows: Maltese mixed, Poodle mixed, and Jack Russell Terrier (5 each); Border Collie and German Shepherd (3 each); Chihuahua (2); crossbreed (7); and Silky Terrier, Labrador Retriever, Pomeranian, Miniature Schnauzer, Cavalier King Charles Spaniel, Greyhound, Cairn Terrier, Dalmatian, Australian Kelpie, Australian Koolie, Nova Scotia Duck Tolling Retriever, German Shorthaired Pointer, Staffordshire Bull Terrier,

German Spitz, Border Terrier, Blue Heeler, and Mastiff (1 each).

Fecal samples were positive for *Campylobacter* spp. in 13 of 27 of the APN cases compared with 11 of 47 cases in the control group. Of the positive cases in the APN group, 2 were positive by PCR only and the remainder tested positive by both methods (PCR and culture). None of the APN cases was positive by culture only. In the control group, 3 dogs had positive *Campylobacter* culture, 6 had positive PCR, and the remaining cases had both positive culture and PCR. Within the APN group, median time from onset of clinical signs to fecal sample collection was 4.5 days (range, 1–11 days) in the *Campylobacter*-positive cases and 11 days (range, 2–20 days) for the negative ones. Most fecal samples from positive APN cases (12/13) were collected within a week of onset of clinical signs. One positive dog presented 11 days after onset of clinical signs, according to the history provided by the owner. Overall, APN cases had 3 times the odds of having had a recent laboratory-confirmed episode of campylobacteriosis compared to control dogs. As the case definition was tightened, the strength of the association between detection of campylobacteriosis and APN increased markedly and was significant when only cases with diagnostic delays <10 days were considered (see Table 1). With a case definition that included only of cases with diagnostic delays of <7 days, APN cases had 9.4 times higher odds of a recent laboratory-confirmed episode of campylobacteriosis compared to control dogs (*P* < 0.001).

Sequencing was available in 10 of 13 *Campylobacter*-positive cases in the APN group, showing that 60% of the samples were classified as *Campylobacter upsaliensis* and 40% as *C. jejuni*. In the control group, DNA sequencing was available from 5 of 11 of the *Campylobacter*-positive cases showing that 80% were classified as *C. upsaliensis* and 20% as *C. jejuni*. No *C. coli* was isolated from any dog in our study.

Univariable exact logistic regression results including OR, and their CI and *P*-values, for each of the explanatory variables considered for associations with case-control status are presented in Table 1. Age, weight, and sex were not statistically significant (*P* = 0.37, *P* = 0.089, *P* = 0.90, respectively). Interestingly, in the univariable analysis, breed size was found to be significantly associated with APN case status (*P* = 0.024), with the most pronounced effect being an association with small breeds.

Questionnaires from owners were returned for 24 of 27 of APN cases and for 47 of 47 of the control group cases. However, based on their history in the clinical database, details relative to the diet were available for all APN cases. Twenty-six (96.3%) of the APN cases were fed raw chicken, mainly chicken necks and wings. Owners of APN cases had 70.7 times higher odds of reporting that their dogs consumed raw chicken than owners of control dogs (*P* < 0.001). The only APN case that was not fed raw chicken had daily contact with live chickens. Among the *Campylobacter*-positive dogs with APN, all had raw chicken in their diet (13/13). No association between other risks factors and the disease was found apart from raw poultry in the diet. Among the

**Table 1.** Descriptive statistics and comparison of 27 acute polyradiculoneuritis cases and 47 controls by exposure variable and univariable exact logistic regression from a case-control study, March 2015 to February 2017, Australia.

Explanatory Variable	Category	APN Group	Control Group	Odds Ratio <sup>a</sup>	95% CI	P-Value
<i>Campylobacter spp.</i> (positive)	Yes	13	11	3.00	0.98, 9.44	0.055
	No	14	36			
<i>Campylobacter spp.</i> (positive <10 days <sup>b</sup> )	Yes	12	11	5.44	1.54, 20.9	0.006
	No	7	36			
<i>Campylobacter spp.</i> (positive <7 days <sup>b</sup> )	Yes	12	11	9.39	2.28, 48.4	<0.001
	No	4	36			
<i>Campylobacter spp.</i> (positive <4 days <sup>b</sup> )	Yes	8	11	12.4	2.07, 136	0.003
	No	2	36			
<i>Campylobacter spp.</i> (type)	<i>C. jejuni</i>	4	1	2.51	0.15, 163	0.87
	<i>C. upsaliensis</i>	6	4			
Raw chicken in diet	Yes	26	12	70.7	9.67, 3,193	<0.001
	No	1	35			
Raw meat in diet	Yes	26	18	40.0	5.60, 1,775	<0.001
	No	1	29			
In contact with birds	Yes	3	6	0.98	0.14, 5.14	1.00
	No	21	41			
Recent vaccination (<6 weeks)	Yes	1	0	1.96	0.05, ∞	0.68
	No	23	47			
Access to water sources	Yes	4	12	0.51	0.11, 1.97	0.43
	No	23	35			
Use of insecticides or weed killers	Yes	8	10	1.83	0.52, 6.32	0.41
	No	16	37			
Tendency to scavenge food	Yes	9	21	0.75	0.24, 2.26	0.75
	No	15	26			
Tendency to scavenge feces	Yes	8	17	0.88	0.27, 2.77	1.00
	No	16	30			
Outdoor access	Yes	8	27	0.37	0.11, 1.15	0.094
	No	16	20			
Rurality of residence	Rural	2	2	2.44	0.16, 37.4	0.54
	Suburban	10	15	1.65	0.51, 5.34	
	Urban	12	30	1.0	(reference)	
Female	Yes	19	31	1.22	0.40, 3.97	0.90
	No	8	16			
Desexed	Yes	20	40	0.50	0.13, 1.94	0.39
	No	7	7			
ANKC breed size <sup>c</sup>	Large	3	9	2.3	0.21, 32.2	0.024
	Medium	2	14	1.0	(reference)	
	Small	22	24	6.2	1.22, 62.8	
Weight (kg) <sup>d</sup>	>20	2	14	1.0	(reference)	0.089
	11–20	6	12	3.38	0.48, 40.3	
	7–10	9	12	5.03	0.81, 56.8	
	<7	10	9	7.31	1.16, 84.0	
Age (years) <sup>e</sup>	Mean (SD)	7.4 (3.6)	6.7 (3.2)	1.07	0.93, 1.24	0.37

<sup>a</sup>Odds ratios (OR), 95% confidence intervals (CI), and *P*-values calculated using exact logistic regression, suited to small datasets. Where zero in 2 × 2 table cells (and ∞ in CIs) median unbiased estimates.

<sup>b</sup>APN cases where sample was collected within 10, 7, and 4 days from onset of clinical signs, respectively.

<sup>c</sup>According to the ANKC categories (<http://ankc.org.au>).

<sup>d</sup>Continuous variable categorized into quartiles to enable exact logistic model to converge.

<sup>e</sup>Continuous variable (units): ORs represent increase in odds of a 1 unit increase in the explanatory variable in APN cases compared to odds in controls.

variables statistically associated with case-control status at *P* < 0.25, “Raw meat in diet,” “Raw chicken in diet,” and “*Campylobacter spp.* positivity” all were considered highly likely to be acting through the same causal pathway (see Fig S1 for putative causal diagrams used to guide multivariable model development). Given our primary interest in estimating the association between *Campylobacter spp.* positivity and APN case status, “Raw meat in diet,” “Raw chicken in diet,” and “Breed

size” dichotomized to represent “Small breed” dogs were excluded from multivariable modeling on the basis that they were not in the minimum adjustment set and that, if included, they would lead to underestimation of the total effect of *Campylobacter spp.* positivity. For completeness, further multivariable models are included in the supplementary materials: a model of APN case-control status including “Raw chicken in diet” and *Campylobacter spp.* positivity (Table S1), models

estimating the association between “Raw chicken in diet” and *Campylobacter* spp. positivity (Table S2) unadjusted and with adjustment for case-control status (considered as estimators of the association between these 2 explanatory variables in the study and source populations, respectively), and a model of APN case-control status including “Small breed” and *Campylobacter* spp. positivity (Table S3).

In our study, 19 of 27 of the APN cases presented with ascending flaccid tetraparesis. Descending tetraparesis was observed in 4 cases, and the remaining 4 cases had all limbs affected at the same time. None of the dogs presented with tetraplegia, paraplegia, or both, although the most were nonambulatory. Only 3 of 27 dogs remained ambulatory over the course of the disease. Dysphonia was reported in 18 of 19 of the dogs and was not documented by owners in the remaining 8 cases. Hyperesthesia was noted in 6 of 27 dogs. Neck ventroflexion was present in 20 of 27 dogs. Respiratory involvement was recorded in 4 of 27 of the dogs, with signs including increased respiratory rate and effort, and paradoxical breathing. Decreased palpebral and gag reflexes both were recorded in only 1 dog. This dog had regurgitation, and thoracic radiographs were unremarkable. Four dogs had experienced diarrhea before the onset of clinical signs. One dog had a history of coughing, and 2 had a history of vomiting before presentation. Two dogs were lost to follow-up. Nineteen (70%) of the dogs recovered from the disease; 11 of 19 recovered completely whereas 8 of 19 recovered up to 80–90% of their normal function as reported by their owners. Six dogs were euthanized, 1 because of deterioration of clinical signs, and 4 based on the owner’s decision despite static clinical signs. One dog experienced relapse of clinical signs. In this dog, relapse occurred after 21 days and the owner elected euthanasia at this stage (Table 2). This dog was positive for *C. upsaliensis*.

The median time to ambulation (>3 steps without support) from onset of the clinical signs was 50.7 days (range, 10–110 days). The median time to reach a plateau (best clinical improvement) was 95.3 days (range, 13–300 days).

A thorough and in some cases repeated tick search was performed and found to be negative in all of the APN dogs. Complete hematology and biochemistry tests were performed in 23 of 27 dogs and included serum CK activity, which was mildly increased in 5 of 23 dogs (range, 508–1,980 U/L; reference range, 50–400 U/L) and serum potassium concentration, which was within the reference range in all of them (23/23). Serum total T4 concentration was measured in 11 of 27 dogs and was decreased in 2 dogs (6 and 16 nM; reference range, 18–40 nM). Acetylcholine receptor antibody was measured in 12 of 27 cases and was negative in all instances. *T. gondii* IFAT was performed in 4 of 27 and *N. caninum* IFAT was performed in 8 of 27 cases, and results were negative in all instances. Antiraccoon saliva antibody was not measured because raccoons are not found in Australia. In the APN group, 7 dogs had lumbar CSF analysis performed. Of these, 3 had albuminocytologic dissociation (protein concentration ranged from 0.82 to 1.48 g/L; reference range, <0.5 g/L).

**Table 2.** Clinical signs, preceding events, and outcome in the 27 dogs with acute polyradiculoneuritis (APN).

		Percentage Present
Clinical features	Ascending LMN tetraparesis	70% (19/27)
	Descending LMN tetraparesis	15% (4/27)
	LMN in all 4 limbs at the same time	15% (4/27)
	Ability to wag the tail	100% (21/21)
	Dysphonia	95% (18/19)
	Neck weakness/ventroflexion	74% (20/27)
	Hyperesthesia	22% (6/27)
	Chest involvement	15% (4/27)
	Facial paresis/paralysis	4% (1/27)
	Regurgitation	4% (1/27)
	Reduced gag reflex	4% (1/27)
	Pyrexia (>39.5°C)	0% (0/27)
	Preceding events	Vomiting and/or diarrhea
Cough		4% (1/27)
Outcome	Complete recovery (100%)	41% (11/27)
	80–90% recovery	30% (8/27)
	Relapse	4% (1/27)
	Euthanasia due to progression of the disease	4% (1/27)
	Euthanasia due to owners’ decision despite static signs	19% (5/27)
	Lost to follow-up	7% (2/27)

LMN, lower motor neuron.

Two had normal CSF analysis, and the remaining 2 showed increased CSF proteins concentration (1.38 and 1.39 g/L) and nucleated cell count (ncc; 9 and 240 ncc/μL, respectively; reference range, <6 ncc/μL). Detailed findings are presented in Table 3. Electromyography (EMG) was performed in 9 of 27 dogs and was abnormal in all of them, suggesting both demyelinating and axonal neuropathy. Fibrillation potentials and positive sharp waves were present in all instances (9/9), as noted on the clinical reports. Complete electrophysiological reports were available for 5 of 9 dogs (Table S4).

## Discussion

We investigated a potential association between *Campylobacter* infection and APN in dogs. Other potential risk factors also were investigated, and a significant association was detected between dogs affected by APN and the consumption of raw chicken (with owners of 96% of APN cases reporting raw chicken consumption, compared to 26% of owners of control dogs). Thus, raw chicken in the diet is highly likely to increase the risk of developing APN in dogs in Australia. In addition, 48% of the dogs with APN were positive for *Campylobacter* infection compared with 23% in the control group. When a stringent case definition was applied (considering only cases in which the fecal sample was collected within 7 days from onset of the clinical signs), APN cases were 9.4 times more likely to have had a recent laboratory-confirmed episode of campylobacteriosis compared to control dogs ( $P < 0.001$ ).

**Table 3.** Additional diagnostic test results in dogs with acute polyradiculoneuritis (APN).

Diagnostic Tests	Results	Incidence
Hematology and biochemistry	Elevated CK levels	22% (5/23)
	Low potassium concentration	0% (0/23)
	Low total T4	18% (2/11)
Lumbar CSF analysis	Albuminocytologic dissociation	43% (3/7)
Serology	Positive IFAT Toxoplasma	0% (0/4)
	Positive IFAT Neospora	0% (0/8)
	Positive Acetylcholine receptor Abs	0% (0/12)
Electrophysiological features	Spontaneous activity in EMG	100% (9/9)
	Decreased CMAP amplitude	100% (9/9)
	F-waves normal	0% (0/4)
	F-waves prolonged	25% (1/4)
	F-waves not detected	75% (3/4)

CK, creatine kinase; T4, thyroxine; CSF, cerebrospinal fluid; IFAT, indirect fluorescent antibody test; Abs, antibodies; EMG, electromyography; CMAP, compound muscle action potential.

Acute polyradiculoneuritis is an immune-mediated polyneuropathy affecting peripheral nerve myelin, axons, or both. The disease is characterized by acute symmetrical ascending motor weakness and hyporeflexia or areflexia.<sup>1-6</sup> The most common presenting clinical signs in our study were ascending flaccid tetraparesis (70%), head and neck weakness (74%), and dysphonia (95%). Six dogs (22%) had a history of gastrointestinal signs before the onset of neurological signs. Cytology of lumbar CSF showed albuminocytologic dissociation in 43% of the cases (3/7) and EMG identified spontaneous activity in all cases, when performed. These findings are consistent with those of other reports.<sup>7</sup>

Previous studies have shown that exposure to racoons was the most common risk factor for dogs to develop APN in North America.<sup>5,6,8</sup> However, it is unclear what triggers the immune response in dogs with no history of exposure to racoon saliva. Association with protozoal infections previously has been suspected.<sup>1</sup> In a retrospective study investigating potential infectious origins, it was suggested that infection with *T. gondii* may trigger APN in dogs,<sup>31</sup> as previously reported in humans.<sup>32,33</sup> However, in a more recent study, only 1 of 14 APN dogs was positive for *T. gondii* Abs.<sup>7</sup> In our study, APN cases tested for *N. caninum* and *T. gondii* all were found to be negative. Moreover, CK activity was within normal limits in most dogs (18/23). The other 5 dogs had mildly increased CK activity, which was interpreted to be a consequence of prolonged recumbency rather than neuro-myopathy. Studies in people have recognized the development of GBS after vaccinations against several pathogens within 6 weeks of receiving the injection.<sup>17-19</sup> Recent vaccination also has been reported as a potential cause of APN in a dog.<sup>34</sup> Only 1 of our APN cases had a history of vaccination within 6 weeks of hospital presentation. Overall,

previous vaccination was not found to be a significant risk factor of APN in our study.

Acute polyradiculoneuritis has been proposed to be the canine equivalent of GBS in humans.<sup>1-7</sup> Both diseases share similarities including clinical signs (acute onset of ascending LMN signs), pathological changes (demyelination of the ventral nerve roots), and, more recently, the presence of serum antiganglioside antibodies.<sup>7</sup> The most frequently identified infectious agent associated with subsequent development of the GBS in humans is *C. jejuni*.<sup>10</sup> Indeed, *C. jejuni* has been isolated in 30% of GBS cases in humans.<sup>35</sup> Molecular mimicry and a cross-reactive immune response play crucial roles in the pathogenesis of GBS. It seems that the lipopolysaccharides from the bacteria contain a ganglioside-like epitope that resembles elements of peripheral nerve gangliosides.<sup>36,37</sup> The relationship between *Campylobacter* infection and APN in dogs is unknown. In a retrospective study,<sup>30</sup> *C. jejuni* was detected by serology (ELISA) in 4 of 44 of the dogs with APN and in 6 of 44 of the control dogs. In contrast, 13 of 27 (48%) of our APN cases were positive for *Campylobacter* infection, based on a combination of fecal culture and PCR from fecal samples. In human medicine, culture is considered the standard for detection of *C. jejuni*.<sup>10</sup> However, fecal culture may be negative even if *Campylobacter* exists in the feces because only a small number of bacteria are present a few weeks after infection.<sup>35</sup> The isolation rate of *Campylobacter* from fecal culture of human patients with GBS ranges from 8 to 50% whereas the detection rate by PCR has been reported to be significantly higher in 1 study.<sup>35,38,39</sup> These results are similar to those of our study where isolation rate of *Campylobacter* spp. from fecal culture in the APN dogs was 41% (11/27). PCR helped detect an additional 2 cases that initially were negative on culture. Serology is more sensitive but less specific than culture-based methods.<sup>10,40</sup> In human medicine, serology for *C. jejuni* uses ELISA with a crude antigenic extract prepared from geographically prevalent *C. jejuni* strains. Because the antigen is crude, and most often a single serum sample is studied, the specificity of the test remains questionable.<sup>40</sup> In infected people, *C. jejuni* has a short median excretion period of approximately 16 days. This finding is similar to that described in dogs.<sup>41</sup> In addition, the variable lag time between acute *C. jejuni* infection and development of GBS is 1-3 weeks in humans. Finally, the number of organisms in the fecal sample, if present, is presumed to be lower when GBS develops as compared to the acute phase of *C. jejuni* infection.<sup>39</sup> Interestingly, among the dogs with APN, the majority of *Campylobacter*-positive samples (92%) were collected and analyzed within 1 week (median, 4.5 days) of the onset of clinical signs whereas for *Campylobacter*-negative samples, the median time from the onset of clinical signs to fecal sample collection was longer (11 days). To account for the likely short shedding period combined with delayed onset of clinical signs, we applied a more restrictive case definition, including only APN cases that were sampled within 10, 7, and 4 days after the onset of clinical signs. We then

found highly significant associations between presence of *Campylobacter* in feces and development of APN ( $P < 0.001$ ), specifically that the dogs with APN were 9.4 times more likely to be positive for *Campylobacter* infection than control dogs when sampled within 10 days of the onset of clinical signs. Therefore, the negative results in our APN group may have been caused by a delay in performing fecal diagnostic tests. However, other possible causes for the 14 negative cases also could be considered, including recent vaccination (1/14) and other unknown infectious agents. Some of these dogs tested seronegative for *N. caninum* (6/14) and *T. gondii* (3/14).

Little literature is available about the prevalence of *Campylobacter spp.* among healthy dogs in Australia. In 1 study from South Australia, a prevalence of 40% percent was observed in healthy dogs (nondiarrheic) although in this study most of the dogs (88%) were unowned strays.<sup>42</sup> Therefore, this study supports previous work suggesting that animals from shelters or commercially kennelled animals have a higher exposure rate to *Campylobacter spp.* than do domestic dogs.<sup>41</sup> To our knowledge, our study is the first to report the prevalence of *Campylobacter spp.* in healthy domestic dogs in Australia and in dogs suffering from APN. Across the groups, *C. upsaliensis* was the most common species isolated in our study, in 10 of 15 (67%) cases where sequencing was available, followed by *C. jejuni* which was isolated in 5 of 15 cases (see Table 1). The prevalence of *Campylobacter spp.* in healthy dogs was 23% (80% *C. upsaliensis*) which is similar to previous studies available from other countries where prevalence ranged from 17 to 59%, with *C. upsaliensis* being the most common isolate. *C. jejuni* accounted for the remainder.<sup>43-45</sup> The prevalence of *C. jejuni* seems to be lower in general in healthy dogs, from 1 to 40% depending on geographical location.<sup>42,44</sup> Most of the studies discussing the link between *Campylobacter spp.* in humans and GBS are based on *C. jejuni*, and therefore, the role of *C. upsaliensis* requires further investigation. To our knowledge, 3 cases of GBS related to *C. upsaliensis* infection have been reported in humans.<sup>46-48</sup> Hence, *C. upsaliensis* appears to be a potential trigger for APN in dogs and GBS in people, although the question remains whether *C. upsaliensis* induces the disease by eliciting an antibody response against an antigen, similar to the mechanism involving *C. jejuni*. The risk of developing GBS after *C. jejuni* infection in people is low (0.1%), suggesting that genetic factors may be involved in triggering the disease.<sup>10</sup> Whether pre-existing antibodies play a role in developing the disease also is unknown. The short duration of *C. jejuni* shedding in dogs suggests that it infects dogs transiently rather than being a commensal organism.<sup>41</sup> In our APN group, the presence of *C. jejuni* was higher than in the control group (40 versus 20%). Although this finding was not significant, *C. jejuni* was 2.5 times more likely to be present among the APN cases than in the control group. The short *C. jejuni* shedding time then would explain why we were only able to isolate *C. upsaliensis* in some of the APN cases.

In our study, consumption of raw chicken meat was strongly associated with the occurrence of APN. Poultry is the most common source of *C. jejuni* infection in

industrialized countries and, in retail surveys, *C. jejuni* is isolated relatively commonly from commercial poultry products.<sup>49</sup> Therefore, contact with or consumption of raw or undercooked poultry products is an important source of exposure to *Campylobacter* strains associated with neurological diseases.<sup>50,51</sup> Results from a study in New Zealand<sup>52</sup> showed that food safety measures to decrease contamination of fresh poultry meat with *Campylobacter spp.* not only decreased incidence of campylobacteriosis but also were associated with decreased incidence of GBS. Transmission of *Campylobacter* may be prevented by improving sanitation, well-cooked poultry products and public health warnings about the hazards of raw chicken consumption. The presence of *C. upsaliensis* in commercial poultry has been reported to range from 1 to 9.7%,<sup>53,54</sup> suggesting that chickens may be a source of emerging *Campylobacter* species.

A significant association was found between small breeds and APN. Based on our clinical experience, small dogs are more likely to be fed raw chicken because of the presence of small bones in the chicken which are easily eaten by these dogs rather than larger meat bones that may be fed to medium and large breed dogs. The association between breed size and APN may be explained by the hypothesis that small dogs are fed chicken necks and wings more frequently than are larger breed dogs. Genetic factors, as suggested in humans with GBS, also may be a factor in any breed differences in the incidence of APN.

Isolation of *Campylobacter* from fecal samples is challenging because of the organism's fragility and short shedding period after infection. Ideally, all samples in our study would have been collected within 10 days after onset of clinical signs to confirm whether the delay in sampling is a factor in negative results in some dogs. Analysis of the raw chicken given to the APN dogs also would have been helpful, but such samples were not available from the owners.

Our study clearly demonstrates that consumption of raw chicken is a risk factor for dogs in the development of APN, and we suspect that *Campylobacter* infection is most likely to be an immunologic trigger as described in humans with GBS.

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## Footnotes

<sup>a</sup> Oxoid microbiology products, Thermo Scientific, Basingstoke, UK

<sup>b</sup> MyTaq Mix, Biorline, MA

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## Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

**Data S1.** Owner's questionnaires for control group in order to collect data relative to the patient's environment and way of living.

**Data S2.** Owner's questionnaires for acute polyradiculoneuritis (APN) group in order to collect data relative to the patient's environment, way of living and natural course of the disease.

**Figure S1.** Putative causal diagrams of APN in dogs used to guide multivariable model development.

**Table S1.** Multivariable exact logistic regression outputs with APN case status as the outcome variable, in a case-control study of 27 APN dogs and 47 control dogs from March 2015 to February 2017 in Australia.

**Table S2.** Univariable exact logistic regression outputs with *Campylobacter* spp. positivity as the outcome variable, in a case-control study of 27 APN dogs and 47 control dogs from March 2015 to February 2017 in Australia.

**Table S3.** Multivariable exact logistic regression outputs with acute polyradiculoneuritis (APN) cases status as the outcome variable, from a case-control study, March 2015 to February 2017, Australia.

**Table S4.** Summary of electrodiagnostic results in the acute polyradiculoneuritis (APN) group.



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