

Environmental risk factors related to the development of canine non-Hodgkin's lymphoma

Fatores de risco ambientais relacionados ao desenvolvimento do linfoma não Hodgkin canino

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ABSTRACT

This research aimed to investigate the possible risk factors associated with the development of canine non-Hodgkin's lymphoma. Owners of 83 dogs with non-Hodgkin's lymphoma and of 84 healthy dogs answered an epidemiological questionnaire. Dogs who lived outside of the house and within 100 meters of busy streets or avenues (defined as more than 50 vehicles per minute) had a higher risk for developing the disease (OR: 3.1, 95% CI: 1.4-6.9, P=0.005). These results suggest that air pollution derived from vehicle traffic may be associated with the development of canine non-Hodgkin's lymphoma.

Key words: pollution, epidemiologic questionnaire, environmental factors, environmental tobacco smoke.

RESUMO

Este trabalho teve como objetivo investigar os possíveis fatores de risco ambientais, associados com o desenvolvimento de linfoma não-Hodgkin nos cães. Um questionário epidemiológico foi aplicado aos proprietários de 83 cães com linfoma não-Hodgkin e 84 proprietários de cães saudáveis. Os cães que viviam permanentemente no lado de fora da casa e em torno de 100 metros de ruas movimentadas ou avenidas (mais de 50 veículos por minuto) tiveram um maior risco de desenvolvimento da doença (OR: 3,1, IC 95%: 1,4-6,9, P=0,005). Esses resultados sugerem que a poluição do ar oriunda do tráfego veicular pode estar associada com o desenvolvimento de linfomas não-Hodgkin canino.

Palavras-chave: poluição, questionário epidemiológico, fatores ambientais, exposição ambiental ao tabaco.

INTRODUCTION

Non-Hodgkin's lymphomas (NHL) are malignant neoplasms that develop in most animal species. They have different histological subtypes and clinical features. NHL are the fifth most common form of cancer in humans and the third in dogs and its etiology is an unknown (FOURNEL-FLEURY et al., 1997; NOGAI et al., 2011).

Environmental factors have been investigated and are suspected in the development of Non-Hodgkin's lymphoma, especially the herbicide 2, 4-dichlorophenoxyacetic acid (GARABRANT, 2002), tobacco smoke (STAGNARO et al., 2004) and air pollution (GAVAZZA et al, 2001; PAZ et al., 2009; MARCONATO et al., 2009; GOUVEIA et al., 2010; MERLO et al., 2010; ABBA et al., 2011; CHAKRABORTY, 2011; KLIUCININKAS et al., 2011; LIOY et al., 2011).

Humans and domestic animals live under similar conditions and might develop similar cancers. Domestic animals are sentinels of potentially dangerous risks of humans due to short latency and, as such, are considered a useful tool for studying the epidemiology of cancer in humans (BACKER et al., 2001; KHANNA, 2006; BREEN

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et al., 2008). This work aimed to conduct a survey in healthy dogs (controls) and in dogs with NHL by means of an epidemiological questionnaire applied to the dog owners, in order to evaluate independent variables that could possibly increase the risk of NHL in dogs.

MATERIALS AND METHODS

Study design

This study is a six-month retrospective case control recorded during March to August 2010. Five clinical, oncology and diagnostic veterinary centers participated in this research: Veterinary Hospital (HOVET) and Department of Pathology of the Faculty of Veterinary Medicine of the University of São Paulo (FMVZ-USP) (west of São Paulo); Veterinary Hospital of the University Anhembi-Morumbi (east); Veterinary Hospital Rebouças (center-west); Veterinary Hospital of the University of Santo Amaro and the Veterinary Oncology – PROVET (both in the south). To examine the impact of a variety of potential risk factors in dogs with non-Hodgkin's lymphoma (NHL), a total of 83 NHL cases and 84 controls were included in the study. Cases of NHL and control group (without neoplasia) were diagnosed by histological and cytological methods (both residing in the same geographical areas and admitted to the same network of hospitals). Exclusion criteria included dogs diagnosed with other types of cancer and dogs diagnosed with more than one type of cancer.

Interviews

Eighty-three owners of dogs with NHL and 84 owners of control dogs were interviewed in person or by telephone using a questionnaire containing epidemiological data of the animal (gender, breed, age), lifestyle (food type, water type, exposure to different substances, proximity to magnetic waves) and data of the owner (lives in house or apartment, address, zip code, smoker or non-smoker, and cigarette type, among others). The questionnaire was applied from March 2010 to August, 2010, as showed in the figure 1 and 2.

Statistical analysis

The association of NHL with possible risk factors was assessed by chi-square test (univariate analysis). Variables that exhibited a p -value ≤ 0.20 were submitted to logistic regression analysis (multivariate analysis) and variables that showed a p -value < 0.005 were considered to be significant. All analyses were performed using SPSS software version 9.0 (SPSS, Inc., Chicago IL).

RESULTS

The mean age for NHL cases was 9.5 years (2-17 years) and 8.5 years (2-15 years) for the controls. There was no association between gender and case/control status. Sixty-one percent of NHL cases ($n=51$) were purebred dogs and 39% were mongrel dogs ($n=32$). Of the control group, 64% ($n=54$) were purebred dogs and 36% were mongrel dogs ($n=35$). The most common canine breeds bearing NHL were: Cocker Spaniel (7%, $n=6$); Rottweiler (6%, $n=5$); Boxer, Bull Terrier, Dachshund and Poodle (5% each, $n=4$); Labrador (4%, $n=3$); Bernese Mountain Dog, Collie, Pit Bull, Irish Setter and Weimaraner (2.5% each, $n=2$); Basset Hound, Beagle, Doberman, Dogue de Bordeaux, Golden Retriever, Siberian Husky, Doberman Pinscher, Schnauzer, Shar-Pei, Fox Terrier and Yorkshire (1% each, $n=1$).

The breeds in the control group were: Poodle (18%, $n=15$); Cocker Spaniel (10%, $n=8$); Yorkshire (6%, $n=5$); Dachshund (5%, $n=4$); Rottweiler, Labrador, Dalmatian, Chihuahua, Boxer and Sheepdog (2.5% each, $n=2$); Staffordshire Terrier, Schnauzer, Doberman Pinscher, German Shepherd, Lhasa Apso, Dogo Argentino, Boston Terrier, Border Collie and Basset Hound (1% each, $n=1$).

All variables showing a score of below $P < 0.20$ from the univariate analysis were included in the multivariate analysis, such as weight ($P < 0.001$), use of Wi-Fi near the dog ($P < 0.001$), living in a house or apartment ($P = 0.01$), use of incense, candles, fragrances, or scented oils ($P = 0.01$), dogs that live inside or outside the house ($P = 0.02$), use of antiparasitic drugs ($P = 0.02$), dogs that live in the same owner's address ($P = 0.03$), exposure to fires or barbecue ($P = 0.03$), contact with insecticides at home ($P = 0.04$), dogs living within 100 meters of a busy street (defined as more than 50 vehicles per hour) ($P = 0.05$), dogs that live on the ground with cement or other material ($P = 0.05$), age ($P = 0.14$), gender ($P = 0.14$), castrated or not ($P = 0.14$), dogs that have contact with herbicides at home ($P = 0.14$) and use of shampoo with insecticide in the bath ($P = 0.2$). From this result, the most statistically significant variables with $P \leq 0.05$ were analyzed together in the multivariate regression analysis.

Multivariable regression showed that dogs who were permanently kept outdoors and lived within 100 meters of busy streets or avenues (more than 50 vehicles per minute) had significantly higher risk for developing NHL (odds ratio 3.1, 95% CI 1.4-6.9, $P = 0.001$) (Table 1). It was also noted that medium and large sized dogs, weighing over 10kg (68%) had

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Epidemiological questionnaire:
CANINE LYMPHOMA: ROLE OF THE ENVIRONMENT

Approved by the Bioethics Committee of the SVMAS – USP (number 1424/2008) in September 8, 2008.

** Name of the Veterinary Clinic or Veterinary Hospital: _____
Number of the chart: _____

1. Owner name

2. Dog's name/age

3. Breed

4. Address () house () apartment

4. ZIP code and name of the neighborhood

6. Does your dog have (or had) lymphoma? yes no

7. Your dog takes water from
 Tap mineral pool
 Rain Lake River

8. Gender of your dog
 female castrated female
 male castrated male

9. Weight of your dog
 ↓10 kg 10-25kg ↑25kg

10. How long has your dog lived with the same owner at the same address?
_____ years _____ months

11. Where does your dog spend 2/3 of his/her time each day?
 In the garden
 Inside the garage of the house
 In an store/shop
 In an industrial area
 Other: _____

12. Does your dog live next to a busy street (10 to 20 thousand vehicles and 1 to 1.3 thousand motorcycles per hour)?
 yes no

13. Your dog lives:
 inside the house only
 inside the house and yard
 in the backyard only
 elsewhere: _____

14. Your backyard has
 grass floor
 Cement plants land _____

15. Your dog lives most of his/her life
 In urban
 In rural

16. You usually do a barbecue or wood burning (fire) in the place where your dog lives
 never 1x/week 2x/week
 3x/week ↑ 3x/week

17. Does your dog have access to building materials containing paint, solvents, formaldehyde, asbestos or other products? No often do not know occasionally rarely If yes, which material? _____

18. Does your dog have contact with herbicide (stored in the garden)
 No often do not know occasionally rarely

19. Does your dog have contact with fungicides (to eliminate fungi, plant diseases due to fungus) which are stored or sprayed on plants in the garden or home?
 No often do not know occasionally rarely

20. Does your dog have contact with insecticides at home, in closets, on the ground, plants or at another location?
 No often do not know occasionally rarely

Figure 1 – Epidemiological questionnaire for pet dog owners – Part 1.

a higher risk for the development of NHL (odds ratio 3.8; 95% , CI 1.8-8.0; P<0.001).

DISCUSSION

Epidemiological data showed that middle-aged and elderly dogs with non-Hodgkin's lymphoma (NHL) (mean age 8.5 years) were the most affected, similar to most studies (FOURNEL-FLEURY et al., 1997; WITHROW et al., 2006; NORTHS et al., 2009). No gender predisposition for the development of NHL was observed like other results (WITHROW et al., 2006; NORTHS et al., 2009). Breed was investigated for the predisposition to the development of NHL, indicating a high incidence in

the Boxer, Bull Mastiff, Basset Hound, Saint Bernard and Bulldog (WITHROW et al., 2007; LURIE et al., 2008; NOGAI et al., 2011), differing from our result measured by the epidemiological questionnaire, in which the most affected breeds were Cocker Spaniel (7%, n=6); Rottweiler (6%, n=5); Boxer, Bull Terrier, Dachshund and Poodle (5% each, n=4) and Labrador (4%, n=3). Although dogs that weigh more than 10kg have a risk of developing NHL, we suggest that this association is not clear, because most dogs with or without lymphoma evaluated in this study were of medium to large size, and weighing over 10kg was not considered in this investigation. The multicentric form of NHL and stages 3 and 4 comprised the greatest proportion, as shown in most of the studies,

<p>21. Is there a wireless (Wi-Fi) in the room where the dog sleeps? <input type="checkbox"/> no <input type="checkbox"/> yes</p> <hr/> <p>22. Is there a cordless phone in the room where the dog sleeps? <input type="checkbox"/> no <input type="checkbox"/> yes <input type="checkbox"/> do not know</p> <hr/> <p>23. Does your dog have contact with household products or biological products used for the maintenance of the house? <input type="checkbox"/> No <input type="checkbox"/> often <input type="checkbox"/> do not know <input type="checkbox"/> occasionally <input type="checkbox"/> rarely</p> <hr/> <p>24. Do you use incense, candles, fragrances, or scented oils where the dog lives? <input type="checkbox"/> No <input type="checkbox"/> often <input type="checkbox"/> do not know <input type="checkbox"/> occasionally <input type="checkbox"/> rarely</p> <hr/> <p>25. Does your dog live in the same environment of people who smoke? <input type="checkbox"/> cigarette <input type="checkbox"/> cigar <input type="checkbox"/> pipe</p> <hr/> <p>26. Does your dog have contact with people who smoke (indoors or in other enclosed spaces or in a car)? <input type="checkbox"/> No <input type="checkbox"/> often <input type="checkbox"/> do not know <input type="checkbox"/> occasionally <input type="checkbox"/> rarely</p> <div style="border: 1px solid black; padding: 2px;"> <p>• Number of packs per day: <input type="checkbox"/> ↓1 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8</p> </div> <p>() Quit smoking? How long? <input type="text"/> years <input type="text"/> months</p> <hr/> <p>27. How many people smoke in the house? <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8</p> <hr/> <p>28. Do you know a dog with lymphoma in your neighborhood? <input type="checkbox"/> no <input type="checkbox"/> yes <input type="checkbox"/> do not know</p> <hr/> <p>29. Do you use shampoo with insecticide in the bath of your dog? <input type="checkbox"/> No <input type="checkbox"/> often <input type="checkbox"/> do not know <input type="checkbox"/> occasionally <input type="checkbox"/> rarely</p> <hr/> <p>30. How many times a year do you treat your dog with some kind of topical antiparasitic drug? <u> </u> x/ year <input type="checkbox"/> never</p> <hr/>	<p>31. What kind of antiparasitic drug do you usually use on your dog? <input type="checkbox"/> None <input type="checkbox"/> Advocate <input type="checkbox"/> Pulvim <input type="checkbox"/> Frontline <input type="checkbox"/> pour-on <input type="checkbox"/> spray <input type="checkbox"/> Flea collars <input type="checkbox"/> Bolfo Talco <input type="checkbox"/> Advantage pour-on <input type="checkbox"/> revolution <input type="checkbox"/> Anti-flea pills (ex: Capstar) <input type="checkbox"/> Other: _____</p> <hr/> <p>32. Do you use these solutions in your house: <input type="checkbox"/> I don't use <input type="checkbox"/> amitraz <input type="checkbox"/> lindane <input type="checkbox"/> other: _____</p> <hr/> <p>33. What kind of food does your dog eat? <input type="checkbox"/> home made <input type="checkbox"/> trade <input type="checkbox"/> both</p> <hr/> <p>34. Does your dog eat (↓ 3x/week) fruits or vegetables? <input type="checkbox"/> no <input type="checkbox"/> yes <input type="checkbox"/> do not know</p> <hr/> <p>35. Someone in contact with the dog works with: <input type="checkbox"/> industry (Which? _____) <input type="checkbox"/> painting <input type="checkbox"/> bodywork <input type="checkbox"/> agricultural <input type="checkbox"/> building <input type="checkbox"/> other <input type="checkbox"/> joinery:</p> <hr/> <p>36. Do you think your dog is exposed to some specific cause that can develop or has developed cancer? Why? _____</p> <hr/> <p>ONLY FOR DOG WITH LYMPHOMA (If you do not know, please ask the vet)</p> <div style="border: 1px solid black; padding: 2px;"> <p>• Location of LYMPHOMA:</p> <p><input type="checkbox"/> Multicentric <input type="checkbox"/> Gastric or intestinal <input type="checkbox"/> Mediastinal <input type="checkbox"/> Cutaneous <input type="checkbox"/> Extra Nodal (renal, neurological, eye, bone, joint, etc.)</p> </div> <hr/> <div style="border: 1px solid black; padding: 2px;"> <p>• Staging:</p> <p><input type="checkbox"/> I only one lymph node involvement. <input type="checkbox"/> II Involvement of multiple superficial lymph nodes, with or without involvement of the tonsils. <input type="checkbox"/> III Generalized Lymphadenomegaly (all involved lymph nodes). <input type="checkbox"/> IV Involvement of liver and / or spleen, with or without lymphadenomegaly widespread. <input type="checkbox"/> V Involvement of blood, bone marrow and / or other organs (eye, skin, etc.) _____</p> </div>
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Figure 2 – Epidemiological questionnaire for pet dog owners- Part 2.

because usually dogs with NHL are treated late, with an advanced stage of disease (FOURNEL-FLEURY et al., 1997; WITHROW et al., 2006).

Most variables had no association with the risk of developing lymphoma. But some variables showed interesting results described below. Exposure to magnetic fields (MF) is reported to be a carcinogenic factor with an increased risk of developing leukemia and NHL in children (HARDELL et al., 2009; ELLIOTT et al., 2010) and dogs that spend 25% of their time outdoors (REIF et al., 2005). Our result showed a relationship between the exposure to Wi-Fi and development of NHL on univariate analysis, but there was no association on multivariate analysis. This

result might be considered a socio-economic factor because most people had Wi-Fi in their house or it was a confounding influence not considered in this investigation. Although there is a strong indication that dogs can be tobacco passive smokers living in the same place with their owner (ROZA & VIEGAS, 2007), this study showed that there is no correlation between exposure to tobacco passive smoke and NHL in dogs, similar to the literature. On the other hand, passive smoker cats showed a higher risk to develop NHL (OR=2.14; 95% CI: 1.2-4.5) (DENSON, 2003).

Air pollution is a serious and growing problem in megacities. This may lead to increased hospitalization for respiratory problems, decreased

Table 1 - Potential risk factors associated with the development of canine lymphoma, São Paulo, Brazil (2010). Multivariate analysis.

Risk factor	OR	CI	P
Dogs kept outdoors near a busy avenue	3,1	1.4 - 6.9	0.005
Weight over 10kg	3.8	1.8 - 8.0	<0.001

immune system, and cell damage caused by toxic components of air, which may contribute to increased risk of developing several types of cancers including NHL (CHAKRABORTY, 2011; KLIUCININKAS et al., 2011; LIOY et al., 2011). Many epidemiological studies in humans showed the association between particulate matter in the air and development of cancer, for example, in Tampa (CHAKRABORTY, 2011), Denmark (RAASCHOU-NIELSEN et al., 2011), Haifa Bay (EITAN et al., 2010), and India (ABBA et al., 2011). Vehicle pollution was the main contributor for benzene concentration in the atmosphere in the study areas (LIOY et al., 2011). Exposure to benzene has a potential to produce chromosome changes and other genetic changes of importance in NHL induction resulting in deletions and translocations (O'CONNOR et al., 1999). Street dust, vehicle exhaust, domestic heating and long-range transport may act not only as a source of particulate matter (PM), but also as a source of particle-bound polycyclic aromatic hydrocarbon (PAHs) and volatile organic compounds (VOCs) (KLIUCININKAS et al., 2011). The increased mortality from NHL and lung cancer in bus drivers and bus maintenance workers may be associated with long-term exposure to urban air pollution in Genoa (KLIUCININKAS et al., 2011). Another study showed association between NHL morbidity and residence near heavy roads ($P < 0.01$) (PAZ et al., 2009).

The city of São Paulo has a significant environmental pollution, mainly caused by fourteen million cars and three million motorcycles (CETESB, 2011). The results of this study suggest that air pollution coming from vehicular traffic may be involved in the development of canine lymphomas, and potentially may also affect human health.

CONCLUSION

There are a few risk factors that have been identified in canine lymphoma. Statistical analysis observed that there is a significantly positive association between dogs that lived outside of the

house around busy streets and avenues and increased risk of malignant lymphoma, suggesting that environmental pollution coming from vehicle traffic may be associated with the disease in dogs in São Paulo city. Considering the dogs as sentinels of humans, this result may be a clue to the development of human lymphoma too, requiring further investigation.

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BIOETHICS

This project was approved by the Ethics Committee of the School of Veterinary Medicine and Animal Science of the University of São Paulo, Brazil, number is 1424/2008.

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