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Association between exposure to farm animals and pets and risk of Multiple Sclerosis

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ABSTRACT

Purpose: There exists inconsistent evidence regarding animals including pets as risk factors for the development of Multiple Sclerosis (MS). We investigated the association between farm animals and pets as possible environmental factors in MS development.
Methods: Population based case-control study with 136 clinically definite MS cases and 272 controls randomly chosen from the community matched on sex and age. Data was collected from both questionnaire and a lifetime calendar detailing residence, occupation and pet/animal exposure over the course of participant's lives.
Results: Exposure to farming, livestock, specific farm animals and remoteness of residence showed no significant association with MS risk. Exposure to cats prior to disease onset was associated with a greater risk of MS (Adjusted Odds Ratio 2.46 (1.17–5.18)) but without a clear dose-response (test for trend, $p=0.76$).
Conclusions: In contrast to other literature, farming and exposure to farm animals were not associated with MS. While we identified an association between cat exposure and MS, there was no dose-response relationship, and previous studies showed inconsistent results, leaving us to conclude that there is no strong evidence that exposure to cats is associated with MS.

1. Introduction

Multiple Sclerosis (MS) is a complex disease of the central nervous system, and aetiological factors continue to be uncovered (Pakpoor and Ramagopalan, 2014). Contagious viral illnesses of pets, such as canine distemper, may potentially be associated with an increased risk of MS. However, immune modulation as a result of exposure to pets could also have a beneficial effect, in line with the "hygiene hypothesis", which proposes that early life infections may down-regulate allergic and autoimmune disorders (Bach, 2001). Inconsistent evidence exists regarding the association between exposure to pets and/or other animals and MS risk (Ghadirian et al., 2001; Bansil et al., 1997; Alonso et al., 2011), but our group recently identified a positive association between farming and exposure to livestock and risk of central nervous system demyelination (Valery et al., 2013). In a population based case-control study in Tasmania, we examined whether farming, and exposure to pets and farm animals prior to the onset of MS was associated with MS risk.

2. Methodology

2.1. Study participants

The population is described in greater detail elsewhere (van der Mei et al., 2003; Ponsonby et al., 2005). People with MS under the age of 60 years were recruited in the state of Tasmania through the use of advertising, information evenings and letters from neurologists. In total, 169 subjects volunteered to participate, while 136 cases were included in the final sample. Thirty (17.8%) did not meet the study protocol with regard to the diagnosis of MS, one person refused a neurological assessment, one person died before the interview took place and one person deteriorated to the extent that the disease became too severe to participate. Case respondents were interviewed and examined by one of the participating neurologists. Magnetic resonance images (MRI) were assessed for 134 of the 136 the cases, and for the other two cases MRI reports from previously conducted scans were obtained. The

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eligible cases had cerebral MRI abnormalities consistent with MS, as defined by Paty et al. (1988) and definite MS using the criteria of Poser et al. (1983) Cases with a classification of primary progressive MS had to exhibit progressive neurological disability for at least one year, had to have no other better explanation for the clinical features, and had to have relevant spinal cord abnormalities and changes on cerebral MRI consistent with demyelination. Controls were selected from the roll of registered electors, a comprehensive listing of the population maintained by the State Electoral Office of Tasmania. For each verified case, two control subjects were randomly selected and matched to the index case on sex and birth year. For the 136 cases included in the study, 272 eligible controls participated with a response rate of 76%.

All participants provided written consent with ethics approval being granted by the Human Research Ethics Committee of the Royal Hobart Hospital.

2.2. Measures

Data was collected by a partly self-completed life and lifetime calendar and a face-to-face interview was conducted by one of two research assistants between March 1999 and June 2001. For each year of their life participants indicated location of residence, the occupation they had, whether they lived at a farm, whether they had any farm animals and whether they had any pets at home that were owned by members of the household, including the type and number of pets. Regarding dog exposure, during the face-to-face interview, the interviewer would ask where the dog would mostly spend its time (mostly outdoors, more outdoors than indoors, more indoors than outdoors, mostly outdoors), how often the participant would cuddle, pat, nurse or stroke the dog (less than 3 times a day, 3–6 times a day, more than 6 times a day) and whether the dog had a disease at a certain stage of life. Residential locations were classified according to the Australian Standard Geographical Classification (ASGC) as a proxy for exposure to a rural environment.

2.3. Data analysis

Using the yearly data from the calendar allowed the calculation of the time (in years) spent in contact with pets prior to the age of first symptom (and the same age for each matched control) or average remoteness index and the calculation of exposure prior particular ages, to examine whether some age periods were of particular importance. Odds ratios and 95% confidence intervals were estimated by conditional logistic regression. We examined a number of factors as potential confounders as they were associated with MS in this dataset (van der Mei et al., 2003; Ponsonby et al., 2005). Farm and pet exposures were adjusted for smoking prior to the onset (no, yes) and time spent in the sun during weekends and holidays before the age of 16 ($\geq$2–3 vs $\leq$1–2 h/day) as e.g those with a cat were less likely to be smokers and more likely to be exposed to the sun. Remoteness variables were adjusted for education level and whether participants had exposure to younger siblings before the age of 6 years ($<$1 yr vs more), as those living more remote were more likely to have a lower education level and high sibling exposure.

3. Results

Overall, 68% of participants were female, and the mean time since diagnosis of the cases was 9.4 years (Table 1). Table 2 shows the association between exposure to various animals and MS. In relation to farm-related variables, no associations were found for being a farmer (only two controls were farmers and no cases), living on a farm, exposure to specific farm animals (cows, sheep, horses, pigs, poultry, goats, sheep dogs, native animals or ferrets), or a variable that combined the individual farm animals into a combined exposure. Cases were more likely to be exposed to cats prior to symptom onset, and this strengthened after adjustment for smoking and sun exposure. However, no dose-response relationship was observed with an increasing duration of exposure to cats (p=0.55). We examined whether there was a specific age period where cat exposure was particularly important. The association became stronger when more years were added in exposure prior to age 10 (OR 1.22 (0.79–1.90)); prior to age 20 (OR 1.41 (0.87–2.29)); prior to age 30 (1.69 (0.99–2.89)), but none were significant. Cat exposure 10 years prior to symptom onset was also not strongly associated (OR 1.50 (0.95–2.40)), while cat exposure during adolescence (age 12–18) was not associated at all (OR 1.12 (0.72–1.75)). The magnitude of association of exposure to cats prior onset did not differ by sex (p-value for interaction 0.77). Exposure to other pets (dogs, birds, Guinea pigs, rabbits) did not differ by case-control status and neither did other dog-related variables, including cumulative time with dogs (in years), the closeness of dogs to the participants (dog inside the home, outside or mixed) and whether the dog/s had suffered illness were not associated with MS. People reported a range of different illnesses for their dogs, including allergy/eczema, bowel problems, cancer/tumour, canine distemper, diabetes, heart disease, hydatids/worms, idiopathic hyperlipidaemia, kennel cough, kidney failure, mange, milk fever, parvo virus, rheumatoid arthritis, skin cancer, and tick paralysis. In relation to childhood exposures, we created variables including exposures prior to the age of 6, 10, 15 or 20 years and during puberty (age 12–18 years), but none were significantly associated with MS. We examined a range of remoteness of residence variables of which three are shown in Table 2. Although cases were slightly less likely to live more remotely, none of the remoteness variables was significantly associated with case status.

Table 1
Characteristics of MS cases and controls.

	MS cases (N=136) n(%)	**Controls (N=272)** n(%)
Female sex, n (%)	92 (67.7)	184 (67.6)
Age, mean (SD) y	43.5 (9.3)	43.6 (9.2)
Age at diagnosis, mean (SD), y	34.6 (9.1)	
Duration of MS since diagnosis, mean (SD), y	9.4 (7.5)	
Duration since first symptoms, mean (SD), y	12.1 (8.0)	
EDSS score, mean (SD)	3.5 (2.2)	
Highest Education, n (%)		
University	25 (18)	41 (15)
Year 12/Tafe/trade	44 (33)	73 (27)
Year 10 or less	66 (49)	155 (58)
Remoteness classification at birth, n (%)	3 (2.2)	8 (2.9)
Major City		
Inner Regional	77 (56.6)	130 (48.0)
Outer Regional	50 (36.7)	126 (46.5)
Remote or very remote	6 (4.4)	7 (4.1)
Smoker before diagnosis, n (%)	85 (63)	143 (53)
History of infectious mononucleosis, n (%)	35 (25.7)	39 (14.3)
$\geq$1 year of time with younger sibling before age 6 years	62 (46)	174 (64)
HLA-DR15 genotype, n (%)	79 (58.1)	66 (28.5)[a]

[a] N=232.