

A case control study of environmental risk factors in Indians with multiple sclerosis

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Abstract

Multiple sclerosis (MS) is a multi-factorial disease with different epidemiological patterns in various populations. The prevalence of MS in India is low and the climatic and environmental situation is much different from countries where MS is more common. The objective of the study was to evaluate environmental and other risk factors of MS patients in India. A total of 63 cases of clinically definite MS and equal number of age and sex matched controls were studied. The study subjects were interviewed by a physician and a social worker with a questionnaire containing the various risk factors. The study showed that there was significant association in history of childhood mumps, contact with dogs, daily consumption of dairy products and positive history of autoimmune diseases among Indians with MS.

INTRODUCTION

Multiple sclerosis (MS) is a disabling neurological disease affecting the young and is regarded as an organ specific inflammatory disease resulting from an aberrant immune attack on myelin or myelin-producing oligodendrocytes present in the central nervous system. There is incomplete understanding of the basic mechanisms of initiation and progression of MS. However, it is widely accepted that some environmental factors trigger the process.¹⁻³ Various studies also suggest geographical location affect the prevalence of the disease.¹⁻³

It is currently believed that genetically susceptible people who are exposed to some environmental factors may develop MS over a period of time.^{4,5} Hence the study of predisposing factors and clinical features of MS in different populations can provide important clues in determining the probable causative factors. Viral infections^{6,7}, wheat consumption^{8,9}, dairy product consumption^{10,11}, fish intake¹², animal fat intake¹², high ultraviolet radiations¹³, Vitamin D¹⁴ are some of the factors that have been studied in various populations.

The prevalence of MS in India is of the order of less than 5 per 100,000.¹⁵ The clinical features of MS in India are similar to those in high prevalence regions.¹⁶ The environmental risk

factors have been studied in detail in the high prevalence regions, but limited information is available about the factors operating in India. The present study aimed as preliminary study to determine the predisposing factors of MS in India.

METHODS

Patients

A total of 63 patients with MS were selected from two centers in Maharashtra state of India. All patients were reviewed and diagnosis confirmed by a neurologist. The patients were required to fulfill the clinically definite multiple sclerosis based on Poser's criteria.¹⁷ Investigations was performed to support the diagnosis of MS, and to exclude other diseases. CSF analysis for oligoclonal bands, visual evoked potential, brainstem auditory evoked potential, and MR imaging were done in some patients. These patients were interviewed by a physician and a social worker wherein a questionnaire was administered.

Controls

A total of 63 age and sex matched healthy controls were selected. The controls were also interviewed by the same physician and social worker wherein the questionnaire was administered.

Questionnaire

The questionnaire contained questions on demographic data, brief history of the disease course as well as the exposure to the various risk factors. The questions included: 1) age at onset of the illness, 2) sex, 3) symptoms and signs at the onset, 4) smoking habits: duration and number of cigarettes smoked daily, 5) contact with pets and duration of contact with pets, 6) history of consumption of dairy products: frequency and quantity, 7) history of allergy to egg, drugs, milk products, sea food and other vegetables, 8) family history of MS, Graves disease, vitiligo, insulin dependent diabetes mellitus, irritable bowel syndrome, and rheumatoid arthritis, 9) past history of measles, mumps, chicken pox and other viral illnesses.

Statistical analysis

Analysis was carried out to determine differences in exposure between MS patients and the control group. Data entry and coding was done by a statistician. Chi square method was used for statistical significance for difference between MS group and Control group. Also the association between a risk factor and the disease was estimated using odds ratios and their 95% confidence intervals (CI).

RESULTS

There were 41 females and 22 males amongst the MS patients. The male to female ratio was 1:1.9. The mean age for male patients was 43.6 ± 9.6 years (Range 24 to 64 years). The mean age for male control was 40.3 ± 16.2 years (Range 12 to 76 years). The mean age for female patients was 42.7 ± 13.2 years (Range 16 to 79 years). The mean age of control at 38.7 ± 21.0 (Range 19 to 79 years). The difference of the ages between the patients and controls for both the males and females were not statistically significant.

Thirty two percent of patients had their first attack between 25 to 30 years of age which was the highest amongst the various age groups. For the symptoms at the onset of illness, 22 of the 63 patients (34%) complained of limb weakness consisting of monoparesis, hemiparesis, paraparesis or quadriparesis; 19 patients (30%) complained of impaired vision; 19 patients (30%) complained of sensory symptoms consisting of numbness or paraesthesia; 8 patients (12%) had incoordination; 4 patients (6%) each complained of diplopia and facial palsy; 2 patients (3%)

complained of tremors and 5 patients (7%) complained of other symptoms such as sphincter disturbance and muscle cramps.

Environmental exposures and other risk factors

Childhood infections: A significantly higher number of MS patients (33%) had history of mumps as compared to controls (14% vs 33%, $p < 0.01$). There were also more measles and chicken-pox among the MS patients as compared to controls, but these were not statistically significant. (Table 1)

Contact with pets: Twenty-six patients (41%) history of contact with pets (defined as close contact for 6 months or more) as compared to 10 of the controls (16%). Significantly more patients (29%) had history of contact with dogs as compared to controls (3% vs 29%, $p < 0.001$). There were also more contact with cats, rabbits and parrots among patients, but there were not statistically significant (Table 2). Out of the 26 MS patients with history of contact with pets, 14 patients had owned the pets for longer than 5 years. The incidence of MS increased significantly with increased duration of exposure to pets.

Family history of MS and other autoimmune diseases: There was a significant increase in the family history of MS and other autoimmune diseases among the patients as compared to controls. Twenty patients (32%) had family history of MS and other autoimmune diseases as compared to 9 (14%) among the controls (Odds ratio of 2.8, 95% confidence interval 1.2 to 6.8; $P < 0.05$). The autoimmune diseases were: Grave disease (5 patients), rheumatoid arthritis (5 patients), vitiligo (3 patients), insulin dependent diabetes mellitus (1 patient), MS (1 patient), others (5 patients).

Smoking: There were 10 smokers, 7 males and 3 females, among the MS patients as compared to 4 smokers amongst the controls. The difference was not statistically insignificant. The frequency of smoking among the patients and controls were listed in Table 3. Among the patients who were smokers, 8 began smoking before the onset of first attack of MS.

History of allergy: Eleven MS patients (18%) had history of allergies to milk products, egg, sea foods, drugs, others such as cereals and vegetables, as compared to 4 among the controls (6%). This

Table 1: Childhood infections among MS patients and controls

Past history of childhood viral infections	Patients (N = 63)		Controls (N = 63)		Odds Ratio (95% CI)
	No	%	No	%	
Chicken pox	25	40	30	48	0.7 (0.4 to 1.5)
Measles	32	51	23	37	1.8 (0.9 to 3.7)
Mumps	21	33	9	14	3.0 (1.3 to 7.2)
Whooping cough	1	2			3.1 (0.1 to 76.3)
Tonsillitis	18	29	10	16	2.1 (0.9 to 5.1)
Others	9	15	3	5	3.3 (0.9 to 13.0)

Table 2: Pet contact among MS patients and controls

Pets	No of patients (N = 63)		No of controls (N = 63)		Odds Ratio (95% CI)
	Exposure	No exposure	Exposure	No exposure	
Cat	5	58	2	61	2.6 (0.5 to 14.1)
Dog	18	45	2	61	12.2 (2.7 to 55.3)
Rabbit	3	60	0	63	7.4 (0.4 to 145.3)
Parrot	4	59	2	61	2.1 (0.4 to 11.7)
Other birds	1	62	3	60	0.3 (0.03 to 3.2)
Other animal	1	62	3	60	0.3 (0.03 to 3.2)

Table 3: Smoking among MS patients and controls

Frequency of Smoking	No. of patients (N = 63)		No. of controls (N = 63)		Odds Ratio 95% CI
	No.	%	No.	%	
5/day or less	5	7.9	2	3.2	2.6 (0.5 to 14.1)
6-10/day	1	1.6	1	1.6	1.0 (0.1 to 16.4)
11-15/day	2	3.2			5.2 (0.2 to 109.8)
16-20/day	1	1.6	1	1.6	1.0 (0.1 to 16.4)
40/day	1	1.6			3.1 (0.1 to 76.3)
Total	10	15.9	4	6	2.8 (0.8 to 9.4)

was not statistically significant (Odds ratio of 3.1, 95% confidence interval 0.9 to 10.4).

Consumption of dairy products: Twenty four patients (38%) had a history of daily intake of milk or other dairy products, as compared to 10 (16%) among the controls. The difference was statistically significant ($p < 0.05$).

DISCUSSION

There is a general belief that in developing countries like India, childhood infections are common, due to social and environmental factors such as over crowding and poor sanitation.¹⁸ Measles, mumps and chicken pox are the common viral infections in childhood. This was seen in patients and controls of the present study. Our study has demonstrated significantly more MS patients with history of mumps as compared to controls. Measles and chicken pox were also more in MS patients than controls, but these were not statistically significant. A previous Indian study has noted overt measles infection to occur significantly more in Indians with MS as compared to controls.¹⁹ Increased risk of MS has been reported to occur with common virus infection like mumps, measles and EBV.²⁰ There were also reports of a large number of other viruses associated with MS, including rabies, scrapie-like agent, carp agent, paramyxovirus, corona virus, Epstein-Barr virus, herpes zoster, herpes simplex, human herpes virus 6, rubella, mumps, canine distemper, Marek's Semliki forest virus, animal and human retroviruses, and human T cell lymphoma virus.²¹⁻²³ In the present study, mumps was the outstanding infection in MS patients.

The frequency of having pet dogs at home was significantly more in MS group than controls in this study, which was consistent with a previous Indian case control study.¹⁹ In our study, the contact with dogs was prolonged in most instances, often being longer than 5 years. Several other previous studies have investigated the relationship between dog exposure and MS²⁴⁻²⁹, with some showing a positive association.²⁴⁻²⁷ The present study also showed an association between exposure to cat, rabbit and parrot among our patients. However, these were not statistically significant. Previous similar studies have shown varying results, with some being harmful and others protective.³⁰ In India, owning a pet is uncommon in the metropolitan environment where this study was done. The socioeconomic status of the dog owners may be higher than the general population.

In our study, there were significantly more autoimmune diseases among the family members of the MS patients as compared to controls. This is consistent with the presently held concepts of genetic risk and autoimmune pathogenesis of MS.³¹⁻³² The risk in siblings and fraternal twins of developing MS is about 2-5%, higher than in the normal population. The risk for identical twins is even higher, at about 30%, demonstrating the importance of genetic factor.⁵ In our study, only one patient had an affected sibling.

Our study found that cigarette smoking was not significantly associated with MS. Smoking as a risk factor has not been previously studied in Indian MS patients. Many studies have demonstrated higher percentage of smokers in MS patients.^{33,34} A recent study done in Norway found that the risk of developing MS among individuals who smoked was nearly twice as high as in non smokers.³³ Nicotine causes a transient worsening of motor function in patients with MS.³⁵⁻³⁷ It has been suggested that nicotine impairs the synaptic transmission in the central nervous system.³⁸ A case control study in England³⁹ on the other hand, showed no significant association between smoking and MS.

In our study, the intake of dairy products was significantly higher in MS patients than controls. Such a correlation has been observed in previous studies.^{10,11} Other dietary products shown to be positively correlated with MS are: a diet high in animal fats¹², high wheat intake^{8,9}, and low fish intake.¹² High ultraviolet radiations¹³ and low vitamin D levels¹⁴ have also been implicated in etiology of MS. On the other hand, we did not find significant correlation between allergy to milk products, eggs, sea foods, medications, cereals and vegetables to development of MS among our patients.

Our study has documented a female preponderance of 1.9 : 1. Six previous Indian studies⁴⁰⁻⁴⁴ have shown a male preponderance (range 1.25-2) while only one Indian study⁴⁵ has shown a female predominance. Our observation of female preponderance is in accordance with most international studies⁴⁷, and probably reflects the changing referral pattern in India. The clinical presentation of our patients is also similar to other previous studies from India.^{47,48}

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REFERENCES

- Poser CM. The epidemiology of multiple sclerosis: a general overview. *Ann Neurol* 1994; 36: 180-93.
- Kurtzke JF, Hyllested K. Multiple sclerosis in Faroe Island: II. Clinical update, transmission and the nature of MS. *Neurology* 1986; 36: 307-28.
- Kurtzke JF, Hyllested K. Multiple sclerosis in the Faroe Islands: I. Clinical and epidemiological features. *Ann Neurol* 1979; 5: 6-21.
- Ebers GC, Sadovnik AD, Risch NJ. The Canadian Collaborative Study Group. A genetic basis for familial aggregation in multiple sclerosis. *Nature* 1995; 377: 150-51.
- Ebers GC. Genetics and multiple sclerosis: an overview. *Ann Neurol* 1994; 36: 12-4.
- Cook SD, Dowling PC. Multiple sclerosis and viruses: an overview. *Neurology* 1980; 30: 80-91.
- Alter M, Zhang-ZX, Davanipour Z, et al. Multiple Sclerosis and childhood infections. *Neurology* 1986; 36: 1386-9.
- Alter M, Yamoor M, Harashe M. Multiple Sclerosis and nutrition. *Arch Neurol* 1974. 31: 267-72.
- Shatin R. Multiple Sclerosis and geography. *Neurology* 1964 ;14 :334-8.
- Malosse D, Perron H, Seigneurin JM. Correlation between milk and dairy product consumption and multiple sclerosis prevalence, a worldwide study. *Neuroepidemiology* 1992; 11: 304-12.
- Agranoff BW. Diet and the geographical distribution of multiple sclerosis. *Lancet*.1974; 1061-4.
- Hutter C. On the causes of multiple sclerosis. *Med Hypotheses* 1993; 41: 93-6.
- Van der Mei IA, Ponsonby AL, Bizzard L, Dwyer T. Regional variation in multiple sclerosis prevalence in Australia and its association with ambient ultraviolet radiation. *Neuroepidemiology* 2001; 20: 168-74.
- Hayes CE. Vitamin D is a natural inhibitor of multiple sclerosis. *Proc Nutr Soc* 2000; 59: 531-5.
- Kurtzke F. MS epidemiology world wide. One view of current status. *Acta Neurol Scand* 1995; Suppl 161: 23-33.
- Bansil S, Singhal BS, Ahuja GK, Ladiwala U, Behari M, Friede R, Cook SD. Comparison between multiple sclerosis in India and the United States: a case control study. *Neurology* 1996: 46:385-7.
- Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis : guidelines for research protocols. *Ann Neurol* 1983; 13: 227-31.
- Ghadirian P, Dadgostar B, Azani R. Case-control study of the association between sociodemographic, lifestyle and medical history factors and multiple sclerosis, A. *Can J Public Health* 2001; 92: 281-5.
- Singhal BS, Wadia NH. Profile of patients of multiple sclerosis in Bombay region. *J Neurol Sci* 1975; 26: 259-70.
- Hernan MA, Zhang SM, Lipworth L, Olek MJ, Ascherio A : Multiple sclerosis and age at infection with common viruses. *Epidemiology* 2001; 12: 301-6.
- Marrie RA, Wolfson C, Sturkenboom MCJM, et al. Multiple sclerosis and antecedent infections: a case controlled study. *Neurology* 2000; 54: 2307-10.
- Sibley WA, Bamford CR, Clark K. Clinical viral infections and multiple sclerosis. *Lancet* 1985; 1: 1313-5.
- Kastrukoff LS, Rice GPA. Virology. In: Paty DW, Ebers GC, eds. Multiple sclerosis. Philadelphia: FA Davis; 1998: 370-402.
- Bansil S, Singhal BS, Ahuja GK. Multiple sclerosis in India: a case-control study of environmental exposures. *Acta Neurol Scand* 1997; 95: 90-5.
- Cook SD, Dowling PC. A possible association between house pets and multiple sclerosis. *Lancet* 1997; 1: 980-2.
- Cook SD, Natelson BH, Levin BE, Chavis PS, Dowling PC. Further evidence of a possible between house dogs and multiple sclerosis. *Ann Neurol* 1978; 3: 141-3.
- Bunnell DH, Visscher BR, Detels R. Multiple Sclerosis and housedogs: A case-control study. *Neurology* 1979; 29: 1027-9.
- Sylwester DL, Poser CM. The association of multiple sclerosis with domestic animals and household pets. *Ann Neurol* 1979; 5: 207-8.
- Read D, Nassim D, Smith P, Patterson C, Warlow C. Multiple sclerosis and dog ownership: A case control investigation. *J Neurol Sci* 1982; 55: 359-67.
- Park K. Principles of epidemiology and epidemiologic methods. In: Park K, ed: Parks textbook of preventive and social medicine. 16th edition. Banarsidas Bhanot Publishers, 2000: 43-106.
- Steinman L. Multiple Sclerosis: A coordinated immunological attack against myelin in the central nervous system. *Cell* 1996; 85: 299-302.
- Noseworthy JH. Progress in determining the causes and treatment of multiple sclerosis. *Nature* 1999; 399: 40-7.
- Riise T, Nortvedt MW, Ascherio A. Smoking is a risk factor for multiple sclerosis. *Neurology* 2003; 61: 1122-4.
- Hernan M, Olek M, Ascherio A. Cigarette smoking and incidence of multiple sclerosis. *Am J Epidemiol* 2001;154:69-74.
- Emre M, De Decker C. Effects of cigarette smoking on motor functions in patients with multiple sclerosis. *Arch Neurol* 1992; 49: 1243-7.
- Franklin CR, Brickner RM. Vasospasm associated with multiple sclerosis. *Arch Neurol Psychiat* (Chicago) 1947; 58: 125
- McAlpine D, Compston ND, Lumsden CE. Multiple Sclerosis, Edinburg: Livingstone, 1995; 61, 156.
- Spillane JD. The effect of nicotine on spinocerebellar ataxia. *Br Med J* 1955; 2 :1345.
- Simpson CA, Newell DJ, Schapira K. Smoking and Multiple Sclerosis. *Neurology* 1966; 16: 1041-3.
- Chopra JS, Radhakrishnan K, Sawhney B. Multiple sclerosis in North West India. *Acta Neurol Scand* 1980; 62: 312-21.
- Gourie Devi M, Nagaraja D. Multiple sclerosis in South-India. In: Kuroiwa Y, Kurland LT, ed: Multiple

- sclerosis east and west. Kyushu University press Fukuoka, Japan 1982; 135-47.
42. Mathew NT, Mathai KV, Abraham J. Incidence and pattern of demyelinating disease in India. *J Neurol Sci* 1971; 13: 27-38.
 43. Verma NP, Ahuja JK: Spectrum of multiple sclerosis in Delhi region. *J Assoc physicians India* 1982; 30: 421-2.
 44. Gangopadhyay G, Das SK, Sarda P, *et al.* Clinical Profile of Multiple Sclerosis in Bengal. *Neurology India* 1999; 47 :18-21.
 45. Deepak A, Raju F, Arjundas G. Multiple sclerosis in south India. Proceedings of the Institute of Neurology. Madras 1983; 12: 59-74.
 46. Kurtzke JF, Beeba GW, Nagler B, *et al.* Studies on natural history of multiple sclerosis. Clinical features of the onset bout. *Acta Neurol Scand* 1968; 44: 467-94.
 47. Bhatia M, Behari M, Ahuja GK. Multiple sclerosis in India: A.I.I.M.S. experience. *J Assoc Physicians India* 1996; 44: 765-7.
 48. Pandit LR, Subramanya R and Rao SN. Multiple sclerosis in coastal Karnataka. *Neurol India* 1993; 41: 143-6.