NEUROLOGY 2003;61:1032–1034

Editorial

Environmental risk factors in multiple sclerosis

Causes, triggers, and patient autonomy

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A coherent consensus regarding the etiology of multiple sclerosis (MS) and immune-mediated chronic diseases (such as rheumatoid arthritis, juvenile diabetes, and autoimmune thyroid disease) has emerged over the past two decades: exogenous (including infectious), environmental, or behavioral (lifestyle) factors cause disease onset in genetically susceptible persons.[1] Neither genes by themselves nor exogenous factors alone are sufficient to cause MS. The likely scenario is that, in a genetically susceptible person, the equilibrium among components of the trimolecular complex (major histocompatibility complex molecules, T-cell receptors, and foreign or self antigens) is disrupted sufficiently to induce a chronic state of autoimmune damage.[2] Despite theories, however, no infectious agent has been established as a causal agent in MS. An environmental etiology for MS is suggested by the strong north–south gradient in disease frequency, by disease clusters, and by evidence that migration to and from high-risk areas in early life influences the likelihood of developing MS.

More sophisticated investigations regarding lifestyle factors associated with MS have recently emerged. Smoking appears to have important but modest associations with MS and other autoimmune disorders; the basis for this association is not yet clear. Riise et al., in this issue of *Neurology*, identified a nearly twofold risk of developing MS in ever smokers in a population-based study of prevalent cases of MS from one region in Norway.[3] Importantly, this risk was not substantially reduced when an indirect measure (education level) of socioeconomic status was included in multivariate modeling. Very similar increased risks have been reported in four other population-based studies (table).[4-7] The magnitude of the associations with cigarette smoking has been modest, but in addition to an association with having ever smoked, several studies appear to support a dose-response relationship between smoking and MS. These four studies used incident rather than prevalent cases of MS, thus reducing potential bias concerning the timing of exposure and its relationship to the timing of disease onset. Tar and nicotine may be important immunotoxic components in cigarette smoke.[8] Both the smoke itself, as well as nicotine, may impair antigen-mediated signaling in T cells.[9] Smoking has been associated with other immune-mediated disorders, including rheumatoid arthritis.[10]

Beyond smoking, diet has also been a behavioral risk factor of interest since two early ecologic studies suggested an association between high fish intake and lowered risk of MS[11] and between high animal fat-based caloric intake and increased risk of MS.[12] Whether specific components of diet can alter risk for developing any chronic disease is extremely difficult to study. Retrospectively collected dietary history for intake patterns that occurred 10 to 20 years prior to disease onset may be plagued by imprecise recall. Increased linoleic acid intake, but not other specific fat sources, has been associated with lower MS risk (RR = 0.3, 95% CI 0.1 to 1.1) in a prospective cohort study.[13] Linoleic acid supplementation can also lessen the severity of experimental allergic encephalomyelitis in guinea pigs.[14]

Vitamin D has also been considered as a potential risk factor. The latitude effect on MS prevalence may be related to decreasing gradients of sunlight and decreased production of vitamin D. There is strong correlation between regional MS prevalence and ultraviolet radiation levels in Australia.[15] Vitamin D can completely inhibit induction of experimental allergic encephalomyelitis in mice, perhaps by stimulating anti-encephalitogenic cytokines.[16] Finally, vitamin D receptor (the site of vitamin D action) gene polymorphisms are associated with MS in Jap-

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Table *Smoking and the risk of MS: Findings from population-based studies*

Study	Design, location	Smoking measure	Odds ratio (95% CI)
Reference 4	Prospective cohort study of incident cases among British women	> 15 cigarettes/day*	1.4 (0.9–2.2)
Reference 5	Prospective cohort study of incident cases among British women	>15 cigarettes/day*	1.4 (0.9–2.2)
Reference 6	Case-control study of incident cases in Montreal	ever vs never smoked	1.6 (1.0–2.4)
		20–40 cigarettes/day*	1.9 (1.2–3.2)
Reference 7	Prospective cohort study among U.S. women	ever vs never smoked	1.6 (1.2–2.1)
		≥25 pack-years*	1.7 (1.2–2.4)
Reference 3	Case-control study of prevalent cases in Hordaland, Norway	ever vs never smoked (dose response not reported)	1.8 (1.1–2.9)

* Comparison group for cigarette dosage categories is never smokers.

anese[17] but not in Canadian[18] patients. Ongoing work associating vitamin D exposure, ultraviolet irradiation, and MS is under way in Australia, as is research examining dietary vitamin D supplementation as a possible preventive treatment strategy for the disease.

An association between solvent exposure and MS has been reported in some studies, but more recently, no increase in MS incidence was found following organic solvent exposure.[19,20] The risk of developing MS is not established to be affected by other exogenous factors such as physical trauma, vaccinations, or stressful life events.

The environmental factors of most interest to people with MS are modifiable factors that may trigger disease exacerbations. The role of environmental factors in the prognosis of MS has been largely limited to investigations of viral infections and physical trauma as triggers of disease exacerbations. Prospective studies among patients with MS have consistently shown a relationship between viral infections and exacerbations of MS, including a recent study showing a twofold increased risk of clinical relapses following symptomatic upper respiratory tract infections and a 3.4-fold increased risk of exacerbation among those with raised antiviral antibody titres.[21] Despite speculation, credible epidemiologic studies have not shown that physical trauma is a disease trigger.[22]

The quality of life for persons with MS and other chronic diseases is dependent on their perceived ability to maintain autonomy and control.[23] Unproven expensive (removal of mercury amalgam), potentially harmful (e.g., some herbs, large doses of vitamins A or D), or burdensome (gluten-free diet) treatments should be avoided. Smoking, on the other hand, has been associated with transient symptomatic worsening,[24] and randomized trial data have suggested a beneficial effect of polyunsaturated fatty acid intake on rate of MS exacerbations.[25,26] Smoking cessation and eating a diet low in animal fat and rich in polyunsaturated fatty acids and vitamin D foods may be encouraged.

Acknowledgment

The authors thank Dr. Stephen Reingold, National MS Society, and Dr. Annette-Langer-Gould, Stanford University, for their input.

References

1. Oksenberg JR, Barcellos LF, Hauser SL. Genetic aspects of multiple sclerosis. Semin Neurol 1999;19:281–288.
2. Sinha AA, Lopez MT, McDevitt HO. Autoimmune diseases: the failure of self tolerance. Science 1990;248:1380–1388.
3. Riise T, Nortvedt MW, Ascherio A. Smoking is a risk factor for multiple sclerosis. Neurology 2003;61:1122–1124.
4. Villard-Mackintosh L, Vessey MD. Oral contraceptives and reproductive factors in multiple sclerosis incidence. Contraception 1993;47:161–168.
5. Thorogood M, Hannaford PC. The influence of oral contraceptives on the risk of multiple sclerosis. Br J Obstet Gynecol 1998;105:1296–1299.
6. Ghadirian P, Jain M, Ducic S, et al. Nutritional factors in the aetiology of multiple sclerosis: a case-control study in Montreal, Canada. Int J Epidemiol 1998;27:845–852.
7. Hernan M, Olek M, Ascherio A. Cigarette smoking and incidence of multiple sclerosis. Am J Epidemiol 2001;154:69–74.
8. Sopori ML, Kozak W. Immunomodulatory effects of cigarette smoke. J Neuroimmunol 1998;83:148–156.
9. Kalra R, Singh SP, Savage SM, et al. Effects of cigarette smoke on immune response: chronic exposure to cigarette smoke impairs antigen-mediated signaling in T-cells and depletes IP3-sensitive Ca (2+) stores. J Pharmacol Exp Ther 2000;293:166–171.
10. Silman AJ, Newman J, MacGregor A. Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease discordant twins. Arthritis Rheum 1996;39:732–735.
11. Swank RL, Lerstad O, Strom A, Backer J. Multiple sclerosis in rural Norway. N Engl J Med 1952;246:721–728.
12. Alter M, Yamoor M, Harshe M. Multiple sclerosis and nutrition. Arch Neurol 1974;31:267–272.
13. Zhang SM, Willett WC, Hernan MA, et al. Dietary fat in relation to risk of multiple sclerosis among two large cohorts of women. Am J Epidemiol 2000;152:1056–1064.
14. Meade CJ, Mertin J, Sheena J, Hunt R. Reduction by linoleic acid of the severity of experimental allergic encephalomyelitis in the guinea pig. J Neurol Sci 1978;35:291–308.
15. van der Mei IA, Ponsonby AL, Blizzard L, Dwyer T. Regional variation in multiple sclerosis prevalence in Australia and its association with ambient ultraviolet radiation. Neuroepidemiology 2001;20:168–174.
16. Hayes CE. Vitamin D: a natural inhibitor of multiple sclerosis. Proc Nutr Soc 2000;59:531–535.
17. Fukazawa T, Yabe I, Kikuchi S, et al. Association of vitamin D receptor gene polymorphisms with multiple sclerosis in Japanese. J Neurol Sci 1999;166:47–52.
18. Steckley JL, Dyment DA, Sadovnick AD, et al. Genetic analysis of vitamin D related genes in Canadian multiple sclerosis patients. Neurology 2000;54:729–732.

19. Gronning M, Albrektsen G, Kvale G, Moen B, Aarli JA, Nyland H. Organic solvents and multiple sclerosis: a case-control study. Acta Neurol Scand 1993;88:247–250.
20. Mortensen JT, Bronnum-Hansen H, Rasmussen K. Multiple sclerosis and organic solvents. Epidemiology 1998;9:168–171.
21. Edwards S, Zvartau M, Clarke H, Irving W, Blumhardt LD. Clinical relapses and disease activity on magnetic resonance imaging associated with viral upper respiratory tract infections in multiple sclerosis. J Neurol Neurosurg Psychiatry 1998;64:736–741.
22. Kurland LT. Trauma and multiple sclerosis. Ann Neurol 1994; 36(suppl):S33–S37.
23. Somerset M, Peters TJ, Sharp DJ, Campbell R. Factors that contribute to quality of life outcomes prioritized by people with multiple sclerosis. Qual Life Res 2003;12:21–29.
24. Emre M, de Decker C. Effects of cigarette smoking on motor functions in patients with multiple sclerosis. Arch Neurol 1992;49:1243–1247.
25. Dworkin RH, Bates D, Millar JH, Paty DW. Linoleic acid and multiple sclerosis: a reanalysis of three doubleblind trials. Neurology 1984;34: 1441–1445.
26. Bates D, Cartlidge NE, French JM, et al. A double-blind controlled trial of long chain n-3 polyunsaturated fatty acids in the treatment of multiple sclerosis. J Neurol Neurosurg Psychiatry 1989;52:18–22.